Giorgio Cavallini
Gianni Paulis *Editors*

Peyronie's Disease

A Comprehensive Guide

Springer

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Introduction

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Giorgio Franco

1.1 Introduction: A Book Project

The role of books about medical subjects is radically changed after the arrival of the Internet era, which provides extreme updating via online libraries such as PubMed.

Actually the objective of this book is not updating but provoking discussion about Peyronie's disease.

In recent years it has been stated that: "The real etiology of Peyronie's disease (PD) and the mechanisms of formation of the plaque still remain obscure. Although conservative management is obtaining a progressively larger consensus among the experts, surgical correction still remains the mainstay treatment for this condition" [7].

These are the conclusions of 2010 guidelines about PD therapy.

We do not agree with such a statement, even though it is out of any doubt that PD is a difficult to understand disease mainly because it is a disease typical of humans who benefit from reliable experimental models only in recent years [3].

A large amount of literature identified that fibrosis is linked to PD [4], experimental models and laboratory research identified PD as a tumorlike disease [9], and complications of surgery are known and might severely affect erectile function in some cases; on the other hand, no report was found in the literature about a worsening of PD symptoms depending on medical therapy.

Emotional and/or relational problems are present in 50–80 % of PD patients and are more severe in young patients; it has been suggested that treatments aimed at improving PD symptoms may also improve psychological outcomes [6]. Thus, an effective conservative therapy might be particularly welcome in patients <40 years of age. Various treatment modalities have been examined; there is no gold standard

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available for the nonsurgical therapeutic approach. However, multimodal therapy is thought to be a relatively positive and safe approach [5, 8].

Further the increase in the number of the cases reported may reflect an increase of the patients' willingness to seek for medical help and of successfully treating erectile dysfunction with 5-phosphodiesterase inhibitors rather than a true increase of the incidence rate [1].

A great attention has been given to surgery. Because of the variety of ways that PD may present in affected patients, no single, standard, surgical treatment for this disorder has prevailed, and multiple variations of each type of procedure may exist. Surgical outcomes of the most commonly used procedures are not substantially different; therefore, the appropriateness of each treatment option may often depend on disease and patient characteristics (e.g., deformity and erectile function). Surgical algorithms have been published to guide surgeons and patients through the selection of surgical procedures in the absence of conclusive, long-term outcome data. Accumulating data on outcomes associated with established procedures, modifications to these procedures, and new surgical techniques and materials may serve to further guide practice and refine evidence-based selection of the surgical approach [2].

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Anatomy of the Penis, with Special Attention to the Tunica Albuginea and to the Corpora Cavernosa

2

Paolo Turchi

Over the last 30 years, the knowledge of anatomy of the penis have been enhanced and complemented with the possibility of studying drug-induced erections in humans. Knowledge of the anatomical structures of the penis as well as the physiological processes involved in the mechanism of erection is an indispensable prerequisite for understanding the pathophysiology of the erection and of a complex disease such as Peyronie's disease.

The penis is the male organ of copulation, made possible by its erectile ability, and urinary elimination. It is located on the midline of the lower abdomen at the level of the pubic bone, above the scrotum.

2.1 Shape, Position, and Relationships

In the penis, we can distinguish a fixed portion, crural or root, a mobile portion, or body and an enlarged end, the glans.

The *crural* (*root*) is located deep in the anterior perineum, contained in the penile lodge, and directed obliquely upward and forward. It is represented by the early portions of the two corpora cavernosa of the penis and the corpus spongiosum of the urethra, which are, respectively, anchored to the ischiopubic rami and the urogenital trigone. Forward below the pubic symphysis, the corpora cavernosa converge to replace the mobile portion.

The *body*, of cylindrical shape, is covered by the skin and to the state of flaccidity extent, in adults, average 10 cm long and 9 cm in circumference. In a state of erection, it increases in length, volume, and consistency and changes position, rising from the scrotum, on which rests in the state of flaccidity, and approaching the abdomen.

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The *glans* is the distal end of the penis. At the flaccid state, it is totally or partially covered by a fold of skin, the foreskin, from which it remains separated by a virtual space. The glans has a shape of a cone with a large base and a rounded apex, at which the external urethral meatus is located. The base of the glans has a circular and protruding outline, called corona of the glans. The latter is bounded by a circular groove, the balanopreputial furrow, which separates it from the body of the penis. Ventral glans is attached to the prepuce through a small fold of skin called the frenulum of the foreskin.

The penis is an organ made of several distinct tissue layers. The outside of the penis is covered with skin that is continuous with the skin of the surrounding pubic region. Many sensory receptors in the penis' skin allow it to receive sensory stimulation during sexual intercourse. Deep to the skin of the penis is a layer of subcutaneous tissue containing blood vessels and protein fibers that loosely anchor the skin to the underlying tissue.

2.2 Fixation

The penis is kept fixed in its place by an apparatus consisting of the suspensory and fundiform ligaments. The first arises about 5 cm above the symphysis pubis and reaches the back of the penis where it splits into two sheets, surrounding the penis adhering to its end and goes back to being a single beam that extends ventrally in the scrotal septum. The second arises from the symphysis pubis and continues down to the end of the penis, at the point where the two corpora cavernosa stick together.

2.3 Vessels and Nerves of the Penis

The *arterial supply* to the erectile apparatus originates from the internal pudendal artery, which is the final branch of the anterior trunk of the internal iliac artery. This passes dorsal to the sacrospinous ligament at the level of the ischial spine and passes through Alcock's canal. As it emerges, it divides into the perineal and penile arteries, running deep to the superficial transverse perineal muscle and pubic symphysis. It pierces the urogenital diaphragm medial to the inferior ramus of the ischium close to the bulb of the urethra and then divides into three branches—the bulbourethral artery, the urethral artery, and the cavernous artery or deep artery of the penis. It terminates as the deep dorsal artery of the penis. The bulbourethral artery supplies the bulb of the urethra, the corpus spongiosum, and the glans penis. It may arise from the cavernous, dorsal, or accessory pudendal arteries. The urethral artery commonly arises as a separate branch from the penile artery. The cavernous artery (deep artery of the penis) usually arises from the penile artery but may originate from the accessory pudendal. It runs lateral to the cavernous vein along the dorsomedial surface of the crura to enter the erectile tissue where the two corpora fuse; it then continues in the center of the corpora cavernosa.

This artery has tortuous configuration to accommodate for elongation during erection. It may arise from the accessory internal pudendal artery within the pelvis

and thus may be at risk during radical pelvic surgery. On its way to the glans, it gives off circumflex arteries to supply the corpus spongiosum. Distally, the dorsal artery runs in a ventrolateral position near the sulcus prior to entering the glans. The frenular branch of the dorsal artery curves around each side of the distal shaft to enter the frenulum and glans ventrally. To the outer casings of the penis, the external pudendal arteries and dorsal penile arteries are distributed, which run into the dorsal groove of the penis.

Intracorporeal Circulation Arterial blood is conveyed to the erectile tissues in the deep arterial system by means of dorsal, cavernous, and bulbourethral arteries. The cavernous artery (deep artery of the penis) gives off multiple helicine arteries among the cavernous spaces within the center of the erectile tissue. Most of these open directly into the sinusoids bounded by trabeculae, but a few helicine arteries terminate in capillaries that supply the trabeculae. The pectiniform septum distally provides communication between the two corpora. The emissary veins at the periphery collect the blood from the sinusoids through the subalbugineal venous plexuses and empty it into the circumflex veins which drain into the deep dorsal vein. With erection, the arteriolar and sinusoidal walls relax secondary to neurotransmitters and the cavernous spaces dilate, enlarging the corporal bodies and stretching the tunica albuginea. The venous tributaries between the sinusoids and the subalbugineal venous plexus are compressed by the dilating sinusoids and the stretched tunica albuginea. The direction of blood flow would then be from the cavernous artery to the helicine arteries, then sinusoids, post-cavernous venules, subalbugineal venous plexuses, and emissary vein.

The *venous drainage* system consists of three distinct groups of veins: superficial, intermediate, and deep. The superficial drainage system consists of venous drainage from the penile skin and prepuce which drain into the superficial dorsal vein that runs under the superficial penile fascia (Colles') and joins the saphenous vein via the external pudendal vein. The intermediate system consists of the deep dorsal vein and circumflex veins that drain the glans, corpus spongiosum, and distal two-thirds of the corpora cavernosa. The veins leave the glans via a retrocoronal plexus to join the deep dorsal vein that runs in the groove between the corpora. Emissary veins from the corpora join the circumflex veins; the latter communicate with each other at the side by lateral veins and corresponding veins from the opposite side and run under Buck's fascia before emptying obliquely into the deep dorsal vein. The latter passes through a space in the suspensory ligament and between the puboprostatic ligament and drains into the internal iliac veins. The deep drainage system consists of the cavernous vein, bulbar vein, and crural veins. The blood from the sinusoids from the proximal third of the penis, carried by emissary veins, drains directly into the cavernous veins at the periphery of the corpora cavernosa. The two cavernous veins join to form the main cavernous vein that lies under the cavernous artery and nerves. The cavernous vein runs between the bulb and the crus to drain into the internal pudendal vein; it forms the main venous drainage of the corpora cavernosa. The crural veins arise from the dorsolateral surface of each crus and unite to drain into the internal pudendal vein. The bulb is drained by the bulbar vein, which drains into the prostatic plexus.

The *lymphatics* from the penile skin and prepuce run proximally toward the presymphyseal plexus and then divide to right and left trunks to join the lymphatics from the scrotum and perineum. They run along superficial external pudendal vessels into the superficial inguinal nodes, especially the superomedial group. Some drainage occurs through the femoral canal into Cloquet's node. The lymphatics from the glans and penile urethra drain into deep inguinal nodes, presymphyseal nodes, and, occasionally, external iliac nodes.

Nerves Somatic innervation arises from sacral spinal segments S2–4 via the pudendal nerve. The perineal branch of the pudendal nerve supplies the posterior part of the scrotum and the rectal nerve to the inferior rectal area. The pudendal nerve continues as the dorsal nerve of the penis, which runs over the surface of the obturator internus under the levator, runs deep to the urogenital diaphragm, and passes through the deep transverse perineal muscle to run along the dorsum of the penis accompanied by the dorsal vein and dorsal artery. Cutaneous nerves to the penis and scrotum arise from the dorsal and posterior branch of the pudendal nerve. The anterior part of the scrotum and proximal penis is supplied by the ilioinguinal nerve after it leaves the superficial inguinal ring. The pudendal nerve supplies the ischiocavernous and bulbocavernous muscles. It branches into the inferior rectal nerve and the scrotal nerve and continues as the dorsal nerve of the penis.

Autonomic nerves consist of sympathetics that arise from lumbar segments L1 and L2 and parasympathetics from S2–4 (nervi erigentes or pelvic nerve). Lumbar splanchnic nerves join the superior hypogastric plexus over the aortic bifurcation, left common vein, and sacral promontory. From this plexus, right and left hypogastric nerves travel medial to the internal iliac artery to the inferior hypogastric plexus. The pelvic plexus adjacent to the base of the bladder, prostate, seminal vesicles, and rectum contains parasympathetic fibers as well. Nerves from the inferior pelvic plexus supply the prostate, seminal vesicles, epididymis, membranous and penile urethra, and bulbourethral gland.

The *cavernous nerves* arise from the pelvic plexus from the lateral surface of the rectum. These nerves run posterolateral to the apex, mid-portion, and base of the prostate anterior to Denonvilliers' fascia between the posterolateral surface of the prostate and the rectum to lie between the lateral pelvic fascia and the prostatic fascia. The branches from the cavernous nerve accompany the branches of the prostatovesicular artery and provide a macroscopic landmark for nerve-sparing radical prostatectomy. The cavernous nerve leaves the pelvis between the transverse perineal muscles and membranous urethra before passing beneath the pubic arch to supply each corpus cavernosum; it also supplies the corpus cavernosum and penile urethra and terminates in a delicate network around the erectile tissue.

2.4 Structure of the Penis

The penis is made of three separate cylinders of a special type of erectile tissue that are capable of filling with blood and increase in size and consistency, becoming rigid. Each of the three cylinders is covered with a thin layer of thin but tough

connective tissue, being bound together as a group with that same type of tissue. The crura (roots) of the corpora cavernosa attach at the under surface of the ischiopubic rami as two separate structures. Such anatomy prevents the erect penis from sinking into the perineum when faced with an axially oriented vaginal compressive load during intercourse. This unique anatomic arrangement, however, places the penile crus at great danger from crush injuries during blunt perineal trauma.

2.4.1 Corpora Cavernosa of the Penis

The penile erectile apparatus consists of paired vascular spongy organs (corpora cavernosa, so-called because of the thousands of tiny caverns, or open spaces, in the tissue that fill with blood during erection) that are closely attached to each other except in the proximal third.

At the root of the penis, corpora cavernosa are separated while they are joined in the body of the penis. Each cavernous body originates through a root at the respective ischiopubic branch and continues along the same branch, adhering to its periosteum. The two corpora cavernosa then converge at the center, uniting themselves below the pubic arch, and continue to pair like the reeds of a rifle and separate from each other by a connective septum. The septum is incomplete distally, perforated on its dorsal margin by vertically orientated openings in the pectiniform septum that provides communication between the corpora. The union of the two corpora cavernosa constitutes, both dorsally than ventrally, a longitudinal groove. In the dorsal groove, the superficial dorsal vein of the penis runs, while in the ventral one, the corpus spongiosum of the urethra is placed. At the distal end, the two corpora cavernosa become thinner and end with a bevel apex, hooded glans.

The corpora cavernosa are constituted by a fibrous casing, the tunica albuginea (A), and a cavernous, or erectile, tissue (B).

A. The tunica albuginea

The tunica albuginea is a whitish membrane (tunica albuginea is an anatomical term that, in fact, literally means “white cover.”) that forms the fibrous coating of the corpora cavernosa, with about 2 mm thickness composed of dense fibrous connective tissue poor in elastic fibers. The bundles of collagen fibers are arranged in one external longitudinal layer that thins considerably ventrally, near the cancellous urethral, and one inner circular. It covers or wraps around the two corpora cavernosa.

The thickness of albuginea varies from individual to individual and in different locations (greater in the ventrolateral); on average, however, have values ranging from 2 to 3 mm in flaccid penis to 0.5 mm during an erection. The volume increase of CC leads to a tension of the albuginea that on the one hand gets thinner and on the other ensures rigidity typical of the erect penis.

The tunica albuginea consists of layers of collagen which can accommodate a considerable degree of intracavernosal pressure prior to rupture. To function effectively, these fascial layers must provide the penis with a wall container capable of withstanding a high degree of rigidity and axial strength when erect, yet supple

when flaccid. The tunica must be able to elongate symmetrically and increase in girth with tumescence, assuring a straight erection. The tensile strength of the tunica is approximately 1,200–1,500 mmHg, making this fascia one of the most strong in the body. Approximately 5 % of the tunica is elastin which enables the penis to develop elongation. The average volume increase of the erect penis from the flaccid volume is 3-fold with a range from 1.7- to 5-fold. The mechanical properties of the tunica which allow for maximum volume changes of the erect penis are called tunica dispensability. Regions of the tunica with focal poor dispensability cause the erect penis to bend. This focal tunica abnormality in dispensability is called Peyronie's disease. Since the corpora cavernosa are located closely side by side, where the two cylinders touch along the midline, the inner layer forms a band of tissue called a septum. The second layer of the tunica albuginea, also shaped like a tube but twice as large, goes around the pair of the corpora cavernosa. The septum of the deep inner layer attaches along the midline to the top and bottom sections of the superficial outer layer, creating a structure that is almost like an I-beam. In addition, there is another or third layer of connective tissue around the two corpora cavernosa that is even more superficial than the tunica albuginea. It is another tubular layer of tissue, called Buck's fascia, that gives the penis added rigidity when the corpora cavernosa fill with blood during erection. There are no nerve endings in the tunica albuginea, but there are nerve endings in Buck's fascia. Any pain associated with Peyronie's disease comes from stretching or inflammation of Buck's fascia, not the tunica albuginea.

As is typical of most connective tissue in the body, the tunica albuginea does not have a good blood supply; it does not need it for the most part, although this poor blood supply works against it. When injured, the poor blood flow to the tunica albuginea causes it to heal slowly or poorly in some cases. This is critical in understanding how the scar develops in the tunica in the first place and how treatment should proceed.

The normal three-dimensional structure of the tunica affords great flexibility, rigidity, and tissue strength to the penis, which are lost consequent to structural changes in Peyronie's disease.

B. Cavernous (erectile) tissue

The cavernous tissue, or erectile, can be compared to a sponge being formed by gaps of irregular shape (lacunar spaces) incompletely separated by septa of variable thickness. The sinusoids (lacunar spaces) among interwoven trabeculae of smooth muscles and supporting connective tissue. The corpora cavernosa sinusoids are widely communicative and larger in the center of the corpora, having a Swiss cheese appearance. This fact enables the blood within the penis to transfer easily from the top to the bottom of the corpora. This also enables the penis to have a common intracavernosal pressure and a common penile rigidity. The sinusoids are smaller in the periphery and have a grapelike appearance. Peripheral sinusoids have a greater individual surface area than central sinusoids. They receive blood directly from arterioles' sinuous (helicine arteries) which run in the septa and are in the subendothelial location, bearing epithelioid

cells which, flaccid penis, almost completely occlude the vascular lumen. These characteristics aid in the passive process of corporal venoocclusion by sub-tunical venule compression against the tunica albuginea.

The septa that surround the sinusoids are detached from the inner surface of the tunica albuginea and take on a trabecular aspect, branching and forming anastomosis in a very complicated manner. They consist of bundles of collagen and elastic fibers and contain bundles of smooth muscle cells that increase in number in thinner trabeculae. In the septa flow, in addition to the helicine arteries, arterioles, some giving rise to an extensive capillary network whose emulgent veins subsequently flow into the sinusoids. This system has the meaning of a circle nutritive while the system of elicine acts only for the purposes of erectile function. All lacunar spaces are lined with endothelial cells that have secretory function and synthesize factors involved in the regulation of corporal smooth muscle tone.

2.4.2 Corpus Spongiosum of the Urethra

The ventral cylinder is called the "corpora spongiosum" because it is composed of soft and spongy tissue; it has the "urethra" or urinary passage tube running through it from the bladder and ends at the tip of the penis. As the corpora spongiosum nears the end of the penis, it flares out to form the "glans" or head of the penis that looks like a cap on top of the two corpora cavernosa.

The ischiocavernosus is a paired muscle that arises from the inner surface of the ischial tuberosity and inserts into the medial and inferior surface of the corpora. These muscles increase penile turgor during erection beyond that attainable by arterial pressure alone. They are supplied by the perineal branch of the perineal nerve (S3–4).

The bulbospongiosus muscle invests the bulb of the urethra and distal corpus spongiosum. It arises from the central tendon of the perineum. The fibers run obliquely upward and laterally on each side of the bulb and insert in the midline dorsally. The muscle is supplied by a deep branch of the perineal nerve and helps to empty the last few drops of urine and to ejaculate semen.

2.5 Wrappings

The skin covering the penis is thin, movable, and expandable to support an erection; in the distal part of the penile shaft, it folds back on itself to form the foreskin and then continues in the form of a thin, pliable foil covering the glans. A small fold of secondary skin, the frenulum, originated under the urethral meatus esterno and extends along the median raphe to the inner surface of the foreskin. The superficial fascia of the penis (dartos) is a thin sheet of connective tissue with smooth muscle cells and elastic fibers. In it the penile arteries and the superficial dorsal vein shall commence. Beneath the dartos, there is a thin connectival layer, the subfascial tunic, more prominent at the base of the penis.

The deep penile fascia (Buck's fascia) is a thin and resistant sheet, enveloping the two corpora cavernosa, adhering firmly to the albuginea and the corpus spongiosum in a separate compartment. It also wraps the deep dorsal vein, arteries, and dorsal nerves.

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Epidemiology

3

Giorgio Cavallini and Giulio Biagiotti

3.1 Generalities

An increase in PD prevalence has been observed over the years.

Polkey reported 550 cases in 1928 worldwide [31]. Ludvik established a rate of 0.3–0.7 % among all urological patients [23], and Lindsay a 0.4 % rate in Rochester [22]. A 3.2 prevalence rate was determined in the male inhabitants of greater Cologne [38].

The increase in the number of cases reported may reflect an increase of the patients' willingness to seek medical help and of successfully treating erectile dysfunction with phosphodiesterase-5 inhibitors (PDE5i) rather than a true increase of the incidence rate [3]. In fact Smith found histological evidence of PD in 23.6 % of autoptic specimens [37], and Michal [25] found that during phalloarteriography, 20 % of men had the typical deformity of PD; in both cases, the men were unaware of PD. Therefore, the frequency of PD found incidentally could be considered unchanged over time.

The racial distribution of PD was the following: 77.6 % were Caucasian, 19.4 % were Afro-American and 2.9 % were Hispanic; there were no Asian males in the cohort reviewed [34]. The low incidence of PD in Asian males has been recently confirmed (0.6 %) [36].

PD prevalence is higher in the following conditions.

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3.2 Erectile Dysfunction (ED)

7.9 % of the patients affected by ED had PD. Significant associations between PD and both the longer duration and the increased severity of ED were detected. There were also significant associations between PD and the following socio-demographic risk factors of ED: age, obesity, smoking, duration and number of cigarettes smoked per day. Concomitant diseases and medical comorbidities such as diabetes, dyslipidaemia, psychological disorders and the presence of at least one risk factor were significantly associated with PD in patients with ED [8]. Type 2 diabetes mellitus and PD solely, and together, negatively affect the vascular status of erection. Type 2 DM demonstrated the principal effect; however, the presence of PD has an additive impairment effect on erection and Doppler parameters [10].

As a general rule, ED is associated with loss of smooth muscle cells (SMCs) and with an increase in fibrosis in the corpora cavernosa, in the tunica albuginea and in the septum [16, 44]. Low oxygen tension is regarded as responsible for improved fibrosis [26, 27]. Transforming growth factor β1 (TGF-β1) increases collagen synthesis in human corpus cavernosal SMCs in culture and is induced by hypoxia [27]. Furthermore, hypoxia can induce TGF-β1 expression and inhibit prostaglandin E (PGE) synthesis [26]. Under ischemic conditions, TGF-β1 induces its own mRNA, leading to a further increase in TGF-β1 synthesis that reinforces the development of severe fibrosis [26].

3.3 Ageing

PD was seldom found in teenagers [39], while it achieves an 8.9 % prevalence in men about 70 years old [29].

The penis is composed of two corpora cavernosa and a single ventral corpus spongiosum. Each corporal body consists of a loose trabecular meshwork of muscular and connective tissues. The corpora cavernosa in the young are composed of 40–52 % muscular cells and in the elderly of 10–36 % muscular cells. Collagen increase parallels the decrease of smooth muscular cells because of increased oxidative stress and/or other profibrotic factors [5, 43]. An increased expression of genes regulating transforming growth factor β1 has parallels ageing not only in the corpora cavernosa and in the tunica albuginea [6, 18]. Inducible nitric oxide (iNOS) is overexpressed in aged arteries; and its blockade leads to an increase in fibrosis measured by smooth muscular cell/collagen ratio. However, iNOS induction and nitric oxide production induce reactive oxygen species (ROS) which lead to fibrosis [28].

3.4 Diabetes Mellitus

One of the most studied risk conditions for PD development is diabetes. Epidemiologic papers agree that PD is more frequent in type 2 diabetes patients where its prevalence ranges from 8 % to 20 % [9, 40]. Hyperglycaemia induces an excessive deposition of collagen and extracellular matrix (ECM), accompanied by the loss of functional cells which characterise tissue fibrosis. Fibrosis is due to the

appearance and accumulation of myofibroblasts or to the switch to a synthetic phenotype producing ECM of the original cell components, such as fibroblasts and/or smooth muscle cells in the penis [15]. A similar exacerbation of fibrosis by inducible nitric oxide (iNOS) deletion is seen in diabetic experimental models [19]. Up-regulation of TGF-β1 expression and phosphoactivation of the smooth muscle actin device (Smad) pathway were shown to occur in the penis of diabetic rats.

3.5 Smoking Habit

In addition to genetic predisposition, trauma of the penis and systemic vascular diseases are risk factors for PD. Smoking and alcohol consumption also seem to have some role in the development of the disease [2]. PD prevalence in heavy smokers is higher than in control population: about 7 % [20]. Smoking increases the P-selectin expression in the penile vascular epithelial cells and damages the ultrastructure of the penile cavernous tissue, which may be the main contributors to smoking-induced erectile dysfunction [46]. P-selectin (a low molecular weight protein) seems to contribute to atherosclerotic lesion development and arterial thrombogenesis by forming large stable platelet-leucocyte aggregates which produce and release proinflammatory molecules, including a variety of cytokines, such as TGF-β [33].

3.6 Radical Retropubic Prostatectomy

Radical retropubic prostatectomy increases the prevalence of PD damaging neurovascular bundles. In such a way, a double mechanism could be envisaged for PD occurrence after radical prostatectomy: vascular and/or nerve damage.

Fibrosis induced by arterial damage has been already discussed.

The prevalence of PD after radical retropubic prostatectomy is about 15.9 % in the white race [40].

An experimental study demonstrated that protein expression of collagens I and III was significantly higher in a neurotomy compared with a control group, which is consistent with increased expression of TGF-β1 [7].

Cavernosal nerve damage is associated with corporal fibrosis and loss of SMCs [21]. Penile biopsy after radical prostatectomy has demonstrated replacement of corporal SMCs with collagen [24]. Furthermore, venous leakage developed in bilateral cavernosal nerve resection rats as a result of the early loss of corporal SMCs by neuropraxia-induced apoptosis, followed by fibrosis [1, 11].

3.7 Hypogonadism

Testosterone level is lower in PD patients than in controls; further PD symptoms are more severe in hypogonadic patients [4, 17, 30].

Animal experimental research has presented convincing evidence that testosterone has profound effects on tissues of the penis involved in the mechanism of

erection and that testosterone deficiency impairs the anatomic and physiologic substrate of erectile capacity [42]. Androgen deprivation produces an increased deposition of extracellular matrix both in humans and in animal models [35, 43], mainly via the inhibition of inducible nitric oxide synthase [12, 13]. Transforming growth factor β1 (TGF-β1) expression is inhibited by androgens and is increased by castration in androgen-dependent tissues [32, 14].

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Aetiology and Risk Factors

4

Giorgio Cavallini

4.1 The State of the Art

Discrepancy between autoptic and clinical prevalence (see Chap. 3) associated with the tumour-like nature of Peyronie's disease (see Chap. 5) legitimates the adoption for PD of the two-step model of onset: transformation and progression. This means that some "agents" may induce the onset of the disease from the tunica albuginea via a genomic modification and some others may induce the volumetric increase of the plaque until the clinical appearance of PD via replication of transformed cells.

4.1.1 Transformation

"Transformation" might be elucidated in the following terms.

The strict racial distribution of PD (see Chap. 3) suggests a genetic aetiology.

Recently a genome-wide association study was performed and identified nine genetic loci containing common variants associated with Dupuytren disease (DD). Seven of these loci mapped within or near genes of the canonical WNT2 locus and each locus yielded relatively large odds ratios (ORs) for DD disease status. Later it has been found that WNT2 is a susceptibility locus for PD and these findings provide evidence for a partly shared genetic susceptibility between PD and DD [4]. Some of the gene families upregulated in both PD and DD were (a) collagen degradation (matrix metalloproteinase (MMP), with MMP2 and MMP9, and thymosins (MMP activators), with TMbeta10 and TMbeta4), (b) ossification (osteoblast-specific factors (OSFs) OSF-1 and OSF-2 (DD only)) and (c) myofibroblast differentiation (RhoGDP dissociation inhibitor 1). The genes upregulated in PD only

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were decorin (an inhibitor of transforming growth factor-beta1 and a part of fibroblast replication/collagen synthesis) and early growth response protein. Reverse transcriptase-polymerase chain reaction confirmed these changes [11, 13].

4.1.2 Progression

PD progression might be elucidated as follows.

Epidemiologic studies indicate that PD prevalence is higher in conditions improving penile fibrosis: diabetes (20.8–8.1 %; there were significant associations between longer duration and poor metabolic control of diabetes and PD) [1, 5, 7], erectile dysfunction (7.1 %) [5–7], smoking habit [9] (7.1 %), ageing (3.6–8.1 %) [12, 14], hypogonadism [3] and radical prostatectomy (15.9 %; younger men and men of white race are at increased risk for PD) [15]. The presence of more than one condition of penile fibrosis leads to a cumulative prevalence of PD [1, 5, 7].

In all cases of increased penile fibrosis as well as in PD-derived fibroblasts, transforming growth factor β1 (TGF-β1) synthesis is increased because of an increased gene expression. TGF-β1 increases collagen synthesis in human corpus cavernosal and tunica albuginea [8]. Thus TGF-β1 gene overexpression and TGF-β1 synthesis are key factors for PD development.

TGF-β1 is mainly synthesized by T cells during the healing process [19]. TGF-β1 is secreted in a latent form associated with LAP (latency-associated peptide). LAP is cleaved to allow the activation of TGF-β1 which is able to bind its receptors TGF-βR1 (transforming growth factor receptor-β1) and TGF-βR2. Therefore, there is a large pool of inactive TGF-β1 in the extracellular environment. Various agents can induce TGF-β1 activation: metalloproteinase MMPs [18], reactive oxygen and nitrogen species (ROS and RNS) [2] and cytokines [10].

The binding of TGF-β1 to its receptors activates the Smad (small mothers against decapentaplegic homologue) signalling pathway which induces the transcription of various genes, including genes encoding members of the extracellular matrix (collagens mostly) [16, 17]. It also activates the differentiation of fibrocytes towards functional fibroblasts.

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Nosology

5

Giorgio Cavallini and Giulio Biagiotti

5.1 PD as an Inflammatory Disease

Microscopic patterns of PD have been defined since the 1960s [6, 33]. The detection of perivascular monocytes and lymphocytes was regarded as a monitor of inflammatory nature of PD [6, 31].

The hypothesis that PD is an inflammation is sustained by biochemical data. Overexpression of inducible (i) nitroxide synthetase (NOS) (which improves in the course of inflammation) [1] and of peroxynitrite (a metabolite of nitric oxide (NO)) occurs in the cavernosal tissue and myofibroblasts of PD patients when endothelial (e) NOS protein is unchanged [32].

An animal model for PD has been developed but produced contradictory results. Cytomodulin (a synthetic oligopeptide with transforming growth factor (TGF)-beta1-like activity) associated with a surgical injury induced a PD-like lesion within 6 weeks after injection into the tunica albuginea of Sprague-Dawley rats [2, 9]. This model demonstrated that iNOS expression is upregulated while eNOS expression is downregulated. However, Ferrini demonstrated that the inhibition of iNOS resulted in the increased deposition of collagen [11] reducing the myofibroblast of the tunica albuginea [36]; on the other hand, an increase of iNOS protects corpora cavernosa from fibrosis [7, 12]. This apparent contradiction may be overcome by the fact that

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iNOS induction and nitric oxide production induce reactive oxygen species (ROS) which lead to fibrosis [21].

Regardless of this contrast, it could be argued that, in PD, NOS alterations probably exist due to impaired cellular respiration (i.e., mitochondrial function) which improves ROS and fibrosis [5].

Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling – they are released by cells and affect the behavior of other cells and sometimes the releasing cell itself. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell. Cytokines regulate mainly immune reaction and inflammation [27].

The expression of proinflammatory cytokines in the tunica albuginea of PD patients compared to those of controls does not show significant difference [25]; on the other hand, pro-immune cytokines are overexpressed [41].

The whole of these data means that it is unlikely an inflammatory nature of PD, since the histological, iNOS, and cytokine data are likely to indicate an immune response toward PD. In fact, as a general rule, inflammation is a stereotypical and phylogenetically primitive mechanism with which the organism reacts toward a variety of agents: chemical, biological, physical, and mechanical. Inflammation is always acute when it begins and subsequently becomes chronic. Collagen deposition is the end stage of the inflammation [27]. Therefore inflammation fits all the following putative etiologies of PD: traumatic, autoimmune, and replicative. As a conclusion, "inflammatory and/or fibrotic disease means undefined disease."

5.2 PD as a Posttraumatic Disease

A significant association between invasive procedures (i.e., urethral catheterization, cystoscopy, and transurethral prostate resection) and PD was found [4]; a significantly higher incidence of penile trauma has been found in both impotent patients and patients with Peyronie's disease compared with controls [16]. The fact that the plaques of PD were found where the strands of the septum are attached in the ventral or in the dorsal aspect of the penis was regarded as indicative of the traumatic origin of PD [8]. Penile trauma has been identified as a risk factor for PD occurrence [3]. On the other hand, some authors have denied that penile trauma may be an etiology for PD [18, 40].

However, trauma does not completely fit with the progressive nature of PD (see natural history), with the exception of considering PD a keloid. In fact scar remodeling and fibroblast proliferation inhibition are lacking in PD (see the paragraph: "PD as a replicative disease").

5.3 PD as an Autoimmune Disease

Humoral and cellular immune responses have been envisaged toward plaque fibroblasts/fibrocytes [28, 30, 34]. Despite numerous studies, there has been no definitive HLA association with Peyronie's disease. Reported family studies suggest a genetic basis for Peyronie's disease but do not indicate a gene closely linked to the HLA complex [17]. By this way, PD is hardly to be recognized as an autoimmune disease. It is more likely that PD is recognized as a "foreign" tissue able to elicit an immune response.

5.4 PD as a Replicative (Tumorlike) Disease

One of the key cellular events in keloid generation is an increased local concentration of transforming growth factor-beta1 (TGFb1) [24]. The synthesis of TGFb1 is increased in PD fibroblasts [10]. TGFb1 regulates a wide range of biological functions including embryonic development, wound healing, organogenesis, immune modulation, and cancer progression. Interestingly, TGF-β is known to inhibit cell growth in benign cells but promote progression in cancer cells; this phenomenon is known as TGF-β paradox [39]. To date, the mechanism of this paradox still remains a scientific mystery. The homozygous wild type of the G915C single nucleotide polymorphism in the coding region of the TGF-beta1 gene, which was recently associated with elevated TGF-beta1 production and pulmonary fibrosis, may influence the predisposition to PD. However, it does not represent a major genetic risk factor [14]. The expression and activity of smooth muscle actin device (Smad) transcription factors of the TGFb1 pathway is increased in fibroblasts of patients with Peyronie's disease [13] as well as in keloid-derived fibroblasts [38]. Monocyte chemotactic protein-1 (MCP-1) is increased in the course of stimulation of cultured PD fibroblasts with TGFb1 [35].

Some DNA modifications have been found in PD fibroblasts. It has been demonstrated that a high frequency of microsatellite alterations and a loss of heterozygosity are associated with PD, suggesting their possible role in the pathogenesis of the disease [26]. Further epigenetic modifications, such as histone acetylation/deacetylation, have been shown to play a role in the pathogenesis of Peyronie's disease [29]. These conditions occur in the majority of human tumors [15].

Cultured and transplanted cells from PD plaques display a behavior similar to tumor cells. The successful establishment of immortalized cell lines from plaques and normal tunica albuginea from men with PD has been obtained. The findings indicate a potential role for basic fibroblast growth factor (FGF) overexpression [22].

The fibrotic plaques of Peyronie's disease and other localized fibrotic conditions have been considered to be the result of an abnormal wound healing process. The potential role of regulatory disorders of apoptosis in abnormal wound healing may

also play a role in the development of Peyronie's disease. The lower expression of apoptotic genes may cause the persistence of collagen-producing cells which were upregulated for unknown reasons and consequently result in plaque formation [42]. As a matter of fact, alterations of cellular differentiation process have been found in tunica albuginea and in plaques of PD patients [37].

Aberrant P53 pathway protein has been found in plaque-derived fibroblasts. PD plaque-derived fibroblasts have demonstrated cultural immortalization and defunctionalization of P53 protein combined with the appropriated responses of its transcriptional elements; the p53 protein is an important cell cycle regulator and proapoptotic factor, and its aberrant function leads to cell immortalization and proliferation; therefore the role of p53 protein has been identified in several human malignancies [22]. PD fibroblasts have demonstrated tumorigenicity in a severely immune-deficient mouse which confirms that the cells cultured from PD plaque can be biologically transformed [23]. Cells from PD plaques form colonies on soft agar, but this ability is absent in tunica albuginea cells. Colony formation may imply that PD cells are tumorlike cells [37].

Some gene regulations are defective in the cells from plaques of PD patients. MCP-1 was significantly more expressed in PD plaque fibroblasts than in the tunica albuginea of PD patients, which in turn is significantly higher than in fibroblasts from the tunica albuginea of the patients without PD [19]. In the plaque tissue, the genes involved in collagen synthesis, myofibroblast differentiation, tissue remodeling, inflammation, ossification, and proteolysis are upregulated, and genes which inhibit some of these processes and collagenase are downregulated [20].

Conclusions

Literature data allows a holistic perspective for Peyronie's disease classification, indicating its replicative (tumorlike) nature.

1. Plaque fibroblasts are recognized as "foreign" by the organism, and this provokes an immune response which appears as an inflammation.
2. There are genetical and epigenetical differences between plaques and normal albuginea, and genetical differences exist between the albuginea of patients with PD and those without PD.
3. The cells of the plaques are dedifferentiated toward immortalized cells.

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Natural History of Peyronie's Disease

6

Gianni Paulis

6.1 Introduction

Generally, in the medical field, the "natural history of disease" refers to the progression of a disease process, from its beginning to its final clinical end points, in an individual over time, in the absence of treatment [1, 2].

Many diseases have a characteristic natural history, although the length of time and signs of disease may vary from case to case and are influenced by therapeutic measures. After the start of disease, pathological changes then occur without the person noticing them. During the subclinical stage (latency period), the disease is not apparent; however, some early pathological changes may be detectable with diagnostic tests.

Final stages of the natural history of a disease can be development and worsening of symptoms, possible recovery, temporary or permanent disability or death.

Peyronie's disease (PD) is a progressive fibrotic disorder characterised by a collagen plaque involving the tunica albuginea of the penis. Penile curvature, pain, penile deformity and erectile dysfunction are the most common symptoms of this disease. PD is not rare; recent studies indicated a prevalence of 3.2–13.0 % in adult men [3–5]. PD has been established much more frequently in autopsy studies; Smith [6] found histological evidence of Peyronie's disease in 23 % of 100 autopsies [6]. Although most studies have confirmed that the mean age of PD patients is approximately 53–55 years, it should be noted that several studies have shown that as many as 10 % of patients who present with PD are younger than 40 years, including teenagers [7–11].

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Common misinterpretations include the belief that PD is uncommon, affects only older men, lacks possibilities of treatment and usually resolves over time.

The natural course of Peyronie's disease consists of two phases characterised by different symptomatology.

In the early phase, the patient may experience these symptoms or signs: penile pain (most frequently during erection), penile curvature or simple penile deformation (shortening and/or narrowing) without bending and palpable nodule (plaque).

Most patients have a palpable nodule, but some of them are unaware [12].

Sometimes PD can be accompanied by erectile dysfunction (22–54 %) [3, 13–15].

In this initial phase, the inflammatory activity progresses causing rapid plaque growth.

Not all patients affected by PD have penile pain; its incidence varies between 20 and 70 % in the literature [14, 16–19]. However, when penile pain is present, it generally tends to resolve by 12–18 months after the disease onset [13, 20–22].

When penile bending is present (prevalence, 87.8–94 %) [14, 16], this tends to worsen or stabilise during the natural progression of the disease [13, 20].

The second phase of PD starts approximately 12–18 months following disease onset. In the course of this chronic phase, pain typically resolves because acute inflammation attenuates, and penile plaque is most commonly palpable because there is a large production of collagen. Penile plaque becomes firmer (extensive fibrosis) or hard if calcification (prevalence, 34 %) [23] or ossification occurs. Penile ossification [24] that coincides with the end of the disease is a very rare condition; only 34 histologically confirmed cases have previously been reported in the literature [25, 26].

Penile deformity may continue to worsen in some patients, and it rarely improves in this second phase of PD [13, 14]. Erectile dysfunction was reported to worsen during the natural course of the disease by 40–52 % of PD patients [14, 22].

Features associated with progression of PD include concomitant risk factors (diabetes, hypertension, erectile deficiency, previous pelvic surgery, etc.), signs and symptoms of longer than 2 years' duration, Dupuytren's disease, the younger age and calcified plaque [27].

In recent years, the tumour-like nature of PD has been accepted [28–32]. It was demonstrated that younger patients are affected by more aggressive tumours [33–36], mainly because of over-expression of proliferative factors such as Ki-67 and p53 [37, 38]. Similarly in younger PD patients, the disease progression is more rapid.

PD also has a negative impact on patient quality of life, with emotional and relationship problems [39–41] and with associated significant depression (48 % of the cases) [42].

The mean duration of Peyronie's disease is variable (18–36 months); therefore the disease may progress and worsen more slowly for more than 3 years in older patients [43], while it was reported that PD worsening is more probable in the group under 50 years of age. Moreover, there is strong evidence that ageing was a positive predictive factor on the severity of the penile deformity [44] due to the longer duration of the disease. Jarow [45] in his study reported that the mean duration of illness (PD) was 6 years [45].

Though numerous studies have demonstrated that PD is a progressive disease process (with possible severe curvature, shortening of the penis and erectile dysfunction) for many patients, other studies – related to the "natural history" of this disease – concluded

that untreated PD patients generally improve spontaneously. This common belief represents an obstacle to treatment especially in the early stages of the disease; consequently, many physicians have a nontherapeutic behaviour in case of PD. We strongly disagree with this behaviour; however, other authors share our opinion [20, 46–48].

To determine practice patterns regarding PD, LaRochelle and Levine [47] interviewed 98 urologists with specific questionnaire. In their study, the authors reported that 38 % of urologists believed that PD spontaneously resolves in greater than 50 % of cases [47].

6.2 Synthesis of Main Studies Related to the "Natural History" of Peyronie's Disease

6.2.1 Williams and Thomas (1968)

They followed 12 PD patients without any treatment (observation period = 20 months–8 years) [49].

The results of the follow-up were complete resolution (four cases (33.3 %)), improved (five cases (41.6 %)) and unchanged (three cases (25 %)).

The evaluation of patients at follow-up was carried out with the following simple assessments: palpation of the penile nodule, presence of pain and the presence of the curvature.

The same authors (1970), in another study, reported that none of the 21 patients with untreated PD experienced a worsening of their condition [50].

Obviously, it must be considered that in 1968 the penile colour Doppler ultrasound study was not available.

6.2.2 Odiase and Whitaker (1980)

In their retrospective study (observation period = 5 years), the observation results of untreated 19 PD patients were improved (12 cases (63.1 %)), unchanged (3 cases (15.7 %)) and worsened (4 cases (21 %)) [51]. The classification was based only on a consideration of the patients' symptoms and physical findings at follow-up attendances: deformity of the penis on erection, lump in the penis, penile pain during erection, difficulty in performing sexual intercourse, proximal distension and distal laxity of the erect penis.

Similarly for this study, we must consider that in 1980 the use of penile colour Doppler ultrasound study was not always used as a diagnostic procedure for PD.

6.2.3 Gelbard et al. (1990)

In a questionnaire-based study (observation period = 3 months–8 years) [22], they revealed that among 97 untreated PD patients, 13 % experienced a resolution of their symptoms, 40 % had progressive disease, and 47 % had stable symptoms.

Only penile pain seems to resolve spontaneously within 12–18 months in the majority of patients, while only 6 % had pain worsening. However, it should be observed that penile abnormality has never been formally evaluated by a physician and this was a simple questionnaire-based study filled out by the patient.

6.2.4 **Kato et al.** (1997)

They investigated changes of clinical findings of PD over time (observation period = 36.8 months).

They evaluated changes of plaque size, penile curvature and erectile dysfunction in ten PD patients [52]. The mean size of plaques decreased significantly compared with the first examination.

However, penile curvature, pain and erectile dysfunction persisted during the follow-up period in nine patients.

In their study, they considered the plaque area (mm^2), but not the plaque volume (mm^3 or cm^3).

6.2.5 **Kadioglu et al.** (2002)

In their retrospective review of 307 untreated patients with PD (observation period = mean 8.4 months) [15], they observed that PD is progressive in 30.2 % and steady in 66.7 % and spontaneous resolution is rare (3,2 %). Furthermore, "systemic vascular disease" was identified as a risk factor in 67.5 % of the cases (hypercholesterolaemia and diabetes were the most common).

The authors concluded that patients with this risk factor had a significantly higher risk for severe penile deformity.

6.2.6 **Mulhall et al.** (2006)

In a study of 246 untreated patients with PD (observation period = 12 months) [13], they reported that a minority of men (12 %) experienced improvement in penile curvature (mean change = 15°), 40 % remained stable and 48 % had worsened at follow-up (mean change = 22°). At baseline and follow-up, penile deformity was determined following intracavernous injection and by measurement at maximum penile rigidity.

All patients with reported penile pain had improvement and 89 % reported complete resolution at follow-up. Penile length decreased during the 1-year follow-up in all patients (mean 0.8 cm/measurement by stretching the flaccid penis).

It should be observed that in this study the authors did not analyse factors associated with the change in PD deformity.

6.2.7 **Grasso et al.** (2007)

They observed 110 untreated patients affected by PD (observation period = at least 5 years (mean 6.4 years)) [53]. Every 12 months, a follow-up was performed with physical examination and ultrasound study (number, size and plaque location). A significant tendency to stabilisation has been observed in patients over 50 years of age (63 cases). Sixty-eight percent of the patients under 50 years showed a progressive worsening of the disease requiring surgical therapy, while in the patient over 50 years, only 31.5 % required surgery. Totally 36 cases (32.72 % of all) evolved into severe deformation not permitting intercourse (23 patients under 50 years (48.9 %) and 13 over 50 (20.6 %)).

However, it should be noted that these authors considered only the length (cm) of PD plaque to calculate the size of the same.

6.2.8 **Bekos et al.** (2008)

In their study, they evaluated the natural history of PD observing 95 untreated patients (observation period = 12 months) [54]. Follow-up was performed with medical and sexual history, physical examination and penile ultrasonography before and after penile injection. Patients were subdivided into three groups according to ultrasonographic patterns: (A) hyperechoic lesion without acoustic shadow, (B) moderately hyperechoic multiple scattered calcified lesions with acoustic shadows and (C) dense calcified hyperechoic lesions. In A group, reduction of lesions and curvature angle was found in 81.8 % of cases. In B group, plaque and curvature reduction was found in 42.9 % and 34.3 % of cases, respectively. In C group, no ultrasonographic evidence of improvement was found.

The authors indicated that PD is a progressive disease and that an increase of plaque size occurs on average in groups B and C (presence of hyperechogenicity and calcifications); they concluded that spontaneous resolution may be expected in the acute phase of PD but not in the case of stabilised disease.

However, we observed that this study [54] did not include the possibility that the phlogistic zone of PD may be detected also as hypoechoic and/or isoechoic area [55–58].

6.2.9 **Paulis and Cavallini** (2013)

In our recent study about the same topic [14], we observed 82 untreated PD patients (observation period = 18 months). The plaque volume increased in 79 patients (96.34 % of total cases) and the increase in plaque size according to echogenic pattern was greater in those cases with hypoechoic and/or isoechoic component (early stage of PD). Five patients (6.94 % of total cases) had their penile curvature improved, 8 (11.11 %) did not change, and 59 patients (81.94 %) had their curvature increased. In

patients with curvature improvement, the mean change was 5.8°, while in patients in whom curvature worsened, the mean change was 12.3°. In addition, a penile curvature appeared in all ten patients that previously did not have any curvature.

Analysing at follow-up, echo findings of patients with penile curve improved (6.94 % = 5 cases); instead we found that in all five cases the penile plaques were increased in size on average of 114.2 %. Then, even if these patients had improved in penile curvature, the disease (phlogistic area) had really progressed locally. We concluded that the changes of the architectural structure of the penis paradoxically had led to an improvement in penile deformity.

Multivariate regression analysis of this study showed that younger age, "time to presentation", body mass index (BMI), number of cigarettes/day, number of comorbidities and ED were significantly related to the increase of plaque volume. In our study the increase in plaque size resulted greater in case of plaques at the initial stage (active phase).

Conversely Bekos et al. in their study [54] concluded that the plaques in early stage tend to grow less. The same authors, although they affirm that ultrasonography is considered the method of choice in the diagnosis and follow-up evaluation of patients with PD, did not include the possibility that the early phlogistic area of PD may be detected also as hypoechoic and/or isoechoic area [55–58].

This way, Bekos et al. [54] have ruled out a large proportion of patients of the possibility of ultrasonographic diagnosis of the disease or at least not recognising the hypoechoic or isoechoic component of the plaque (early stage of the disease).

We think that the outcomes of Bekos's study differ from ours because these authors didn't consider the early sonographic pattern of PD and they have not properly implemented the precise measurement of the plaque; indeed, they considered only the length of the plaque to calculate the size of the same.

In addition, although these authors concluded that ultrasonographic characteristics may be used to identify the active or the chronic phase of PD, no comparative statistical analysis has been presented, making it difficult to draw conclusions from the outcomes of their study.

6.2.10 **Berookhim et al.** (2014)

In their study, they evaluated the natural history of PD observing 176 untreated patients who opted for no treatment to define predictors of PD deformity stabilisation and improvement (observation period = at least 12 months) [43].

The authors stratified the study population into three groups based on their time to presentation for evaluation after the onset of symptoms: Group A, ≤6 months; Group B, 7–12 months; and Group C, 13–18 months. In all patients, 67 % of these had no change in deformity over time, while 12 % improved with a mean change of 27° (±14 SD), and in 21 % the deformity progressed (worsened) with a mean change of 22° (±11 SD).

These authors concluded that among PD patients, the stabilisation of penile curvature is more likely among older patients and those with a time to initial presentation

of more than 6 months, whereas improvement rates were higher among younger patients and those that underwent a medical examination earlier than 6 months from symptom onset.

Although the authors conducted a very good study, it shows some limitations: the authors assessed only PD patients with uniplanar curvature, excluding multiplanar curvatures and other possible deformities associated with PD (shortening, narrowing, hourglass deformities, indentations and tapering).

While the natural history of the disease may be like these patient populations, however, we cannot use the data of their study to extrapolate results to other types of deformity.

Unfortunately, most of these studies have provided the general data as to the history of PD, and moreover, they did not analyse factors associated with the change in PD deformity and did not consider "time to presentation" as a factor in describing the breakdown of deformity changes.

Differences among the different studies in terms of PD progression should be interpreted as the resultant of different (in terms of risk factors) studied populations.

In addition, most authors in their studies used subjective methods (palpation or questionnaires); instead, they did not perform penile ultrasound and did not examine operator-dependent variability.

Moreover, some authors performed penile ultrasound study but considered only the length of the plaques but not the volume of the same plaques with the three dimensions: length, width and thickness [14].

Several authors, in their studies, did not analyse factors associated with PD progression.

In our latest study on the natural course of the disease [9], the outcomes revealed that PD is a time-dependent progressive disease in the majority of the patients, whose progression appears to be directly linked to the following PD risk factors:

- Overweight and obesity ($p<0.01$)
- Age <45 years ($p<0.01$)
- Cigarette smoking ($p<0.01$)
- *Time to presentation* for medical evaluation after the onset of symptoms (delay) ($p<0.01$)
- Hypertension ($p<0.05$)
- Diabetes ($p<0.05$)
- Previous pelvic surgery ($p<0.05$)
- Erectile deficiency ($p<0.05$)
- Hypogonadism ($p<0.05$)

Our results showed that PD, left untreated, certainly gets worse over time with an increase in plaque volume and this occurs more significantly and faster in younger patients, in accordance with previous studies [12, 53]. Furthermore, PD progression is not linked to the severity of symptoms.

6.2.11 Final Considerations

After a careful evaluation of the literature in this field, it's reasonable to believe that the duration of PD is longer than 18–36 months. Certainly, there is a wide discussion in the topic of the natural history of PD; as a result, there are several points of view [48], which inevitably lead to erroneous conclusions [47]. We believe that the old studies, in the same topic, should not be evaluated for the natural course of PD.

Towards a better understanding of the natural history of PD:

- Studies are needed to evaluate the natural course of PD, not only with subjective parameters but mainly with safe diagnostic tools (penile ultrasound study mainly for evaluation of plaque volume, etc.) because this topic requires certainties and no doubts or incorrect conclusions.
- Multicentre studies have been recommended for retrospective research to allow comparisons among the data of each centre to improve their reliability.
- Future studies on this topic should always consider the risk factors associated with PD progression.
- In order to have a greater statistical significance, future studies that include a large number of PD patients are needed.
- To evaluate the natural course of PD, further retrospective studies with a longer period of observation (period >36 months) are required.

In our opinion, the *natural history of Peyronie's disease* does not mean that this disease heals always spontaneously. In accordance with other studies, Levine [59] in his review article reported that PD does not tend to resolve spontaneously as previously thought and is still considered to occur by many physicians [59].

Considering that several more recent studies have demonstrated low rates of spontaneous resolution [13–15, 54], we believe that PD is certainly a progressive chronic disease process that rarely heals spontaneously.

Consequently, PD should always be treated medically and possibly in the early phase of the disease.

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Experimental Models and Laboratory Research for Peyronie's Disease

7

Tommaso Cai

7.1 Introduction

Notwithstanding its high prevalence and impact on the quality of life of patients, and that it is an excellent model for the study of fibrotic processes, Peyronie's disease (PD) is an orphan disease in basic research [1]. The pathophysiology of PD is considered to be multifactorial, with interactions of genetic predisposition, trauma, tissue inflammation, and aberrant wound healing, without any convincing and unanimous physiopathology. This is due to the fact that there are very few preclinical studies. The number of experimental and animal models is very low even if contributed to the disease physiopathological understanding and has advanced substantially the proposal of new therapies [1].

7.2 Status of the Current Knowledge

Peyronie's disease is a connective tissue disorder of the tunica albuginea. This phenomenon is characterized by changes in the collagen and elastin metabolism and composition of the tunica albuginea [2]. The underlying physiopathological mechanism is still is poorly understood. However, it is well known that PD is an inflammatory process of the tunica albuginea characterized by an increase in and disorganization of collagen fibers, persistent fibrin deposition within the tissue, and elastin fragmentation [3]. At the current time, the experimental model allowed to clarify [1]:

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- The role of microtrauma, myofibroblasts, and oxidative stress in plaque development
- That this tissue has undersustained turnover by fibrotic and antifibrotic mechanisms
- The interplay of collagenolytic and fibrinolytic systems and their inhibitors
- An endogenous antifibrotic process consisting of the expression of inducible nitric oxide synthase that counteracts oxidative stress, collagen synthesis, and myofibroblast generation
- The antifibrotic effects of chronic treatment with phosphodiesterase type 5 (PDE5) inhibitors
- The cytogenetic instability of PD cells and alterations in their gene expression
- The role of stem cells in the tunica albuginea with a potential role in fibrosis and ossification

7.3 Preanimal Model Period

On the basis of observations in human penile tissue, it was suggested that PD plaque is the result from microtrauma to the tunica albuginea, which allows for the accumulation of fibrin into the interstices of the tunica albuginea, ultimately leading to an abnormal wound healing process and formation of a scar [4, 5]. El-Sakka in 1997, for the first time, demonstrated within the PD plaque increased levels of transforming growth factor β1 (TGF-β1), a profibrotic factor [6]. This observation led to the first experimental animal model for this disease [1].

7.4 The "Pioneering" Experimental Model

In 1997, El-Sakka and coworkers injected a TGF-β1-like peptide (cytomodulin) into the rat penile tunica albuginea to produce a PD-like lesion [7]. The injection of cytomodulin into the tunica tissue of rat penis resulted in substantial chronic cellular infiltration, focal and diffuse elastosis, thickening of tunica albuginea, disorganization and clumping of collagen bundles, and expression of TGF b1 isoform [7]. These histological features were observed up to 6 weeks and were similar to that seen in human PD plaque [7]. This is the first animal model in the PD's research history.

7.5 Current Experimental Animal Model

In the subsequent years, some experimental and animal models have been purposed and development without any unanimous physiopathologic opinion. Today, all researches in PD are hampered by the lack of universally accepted animal model, and this is likely attributed to the limited insight into PD mechanisms and the

difficulties faced by current animal models to truly represent the complexity and complete spectrum of human disease. All published animal and laboratory studies can be grouped into four groups:

- TGF-β1 model
- Fibrin model
- Surgical trauma model
- Genetic/spontaneous model

The current animal models on PD are based predominantly on rats due to the fact that (1) the anatomy of the rat penis has been extensively described and this model has sufficiently demonstrated similar morphological and functional characteristics to humans and (2) they are more economical to purchase, house, maintain, and dispose off compared with larger animals [8].

7.5.1 TGF-β1 Model

TGF-β1 is a soluble growth factor of the TGF-β superfamily and binds to specific serine/threonine kinase receptors on cell surface. It is considered as a profibrotic cytochine that is involved in cellular proliferation and/or differentiation, an essential system in the pathogenesis of fibrotic disorder. The TGF-β1 injection is able to induce chronic inflammation and fibrosis in the tunica tissue over time. It is due to its ability to induce its own production that it may be the key to the development of the scarring and fibrosis into chronic, progressive condition [9]. Moreover, El-Sakka demonstrated that the PD-like plaque induced by the TGF-β1 injection was reduced by colchicine, a collagenase and myofibroblasts inhibitor drug [10]. Interestingly, Bivalacqua and coworkers found induction of inducible nitric oxide synthase (iNOS) after the injection of TGF-β1 into the tunica albuginea of rat [11]. They treated 54 male rats with (1) saline injected (0.1 ml) into the tunica albuginea or (2) TGF-β1 (0.5 μg) injected into the tunica albuginea or (3) surgical injury to the tunica albuginea. All rats underwent electrical stimulation of the cavernosal nerve and pharmacological stimulation with acetylcholine, an endothelium-dependent vasodilator, after 6 weeks. After scarified all rats, cavernosal tissue was homogenized and constitutive and inducible NOS enzyme activity. They, by using this model, found that iNOS was significantly higher, and constitutive NOS was downregulated in the corpus cavernosum of the TGF-β1-injected and surgical injury rats after 6 weeks, highlighting a possible mechanism by which some men with Peyronie's disease suffer from erectile dysfunction [11]. The increase in iNOS expression and activity in the fibroblasts propagates the fibrotic cycle and, in the presence of fibrogenic reactive oxygen species, leads to increase in oxidative stress [11]. The role of iNOS seems significant in the physiopathology of PD plaque development. Ferrini and coworkers, in an animal model, found long-term inhibition of iNOS activity with increase in fibrosis and plaque formation when a specific inhibitor of iNOS was given to the rats for 6 weeks following the TGF-β1

injection into the tunica albuginea [12]. In this sense, iNOS induction in this tissue may be a protective mechanism against fibrosis and abnormal wound healing [11, 12]. In this sense, nitric oxide is able to bind to reactive oxygen species, the profibrotic compounds produced by oxidative stress, in a reaction that produces peroxynitrite [1]. Moreover, nitric oxide has been demonstrated that originate iNOS induced within the tunical fibroblasts via transcriptional activation by cytokines [1]. Other authors found that myostatin, a TGF-β family member, in addition to TGF-β1 itself, is overexpressed in the cell cultures of PD plaque and tissues of experimental model of PD [13]. Myostatin is expressed in myofibroblasts and seems to have a profibrotic action. The finding supports this characteristic that in vivo, it elicits a PD-like plaque in the rat tunica albuginea and intensifies the fibrotic process triggered by TG- β1 [1]. On the other hand, TGF-β1 does not require the presence of myostatin to its action [14]. Myostatin does not stimulate stem cells/myofibroblast lineage differentiation per se but upregulates TGF-β1 levels [14]. This mutual interaction between TGF-β1 and myostatin is paramount to the pathogenesis of fibrotic diseases [1]. The role of myofibroblast is significant in PD's plaque formation. Myofibroblasts, in fact, are key cells during wound healing, which, at the completion of this process, are normally eliminated by apoptosis [15]. When they persist, this is abnormal, and such persistence leads to scar formation. Furthermore, the myofibroblasts accumulation in normal tissues is, together with the other discussed factor, a landmark of the development of fibrosis [15].

- *Model advantages*
  1. A single injection is adequate to cause a PD plaque formation.
  2. This model allows for the investigations for therapeutic agents targeted against these molecular targets [8].
- *Model disadvantages*
  1. A long time to plaque formation
  2. Inconsistent plaque that disappears after 60 days
  3. Lack of penile curvature and calcification/ossification [8]

7.5.2 Fibrin Model

Today, the major investigators agree that PD arises following (micro)trauma to the erect penis, presumably from buckling forces during sexual activities [1, 8]. Following injury to the erect penis, there is a localized disruption of the penile tunica albuginea and an increase in microvascular permeability with release of various cytokines and growth factors [1, 8]. On the basis of this theory, there is an initial perivascular inflammatory cell infiltrate with extravasation of blood proteins released following the fracture of the tunica albuginea [1, 8]. In this sense, a significant role should be attributed to fibrinogen/fibrin action. The mechanism of excessive deposition of fibrin is attributed to the persistence fibrin deposition due to unmasking of fibrinolytic enzymes by other plasma proteins and/or deficiency of fibrinolytic enzymes [8]. As suggested by Chung, the persistence of fibrin elicits an acute and, later, a chronic

inflammatory response and subsequent production of profibrotic factors (TGF-β1), and reactive oxygen species induce the development of the fibrotic plaque [8]. In 1997, Somers and coworkers, by using an experimental model on plaque tissue specimens, found that deposition of fibrin in plaque tissue is consistent with the hypothesis that repetitive microvascular injury results in fibrin deposition in the tissue space and has served to provide insights into the pathophysiology of Peyronie's disease [5]. Fibrin is an effective chemoattractant and chemotactic factor and promotes ingrowth of inflammatory cells, macrophages, and fibroblast and induces collagen synthesis by fibroblast [8]. In 2003, Davilla et al. by using a new animal model for PD found that fibrin, when introduced into the tunica albuginea of the rat penis, acts as a potential profibrotic protein, possibly via the local release of TGF-β1, and induces a plaque not only histologically similar to that induced by TGF-β1 but to that of the human condition [3]. The high expression of TGF-β1 supports the hypothesis that fibrin deposition after trauma to penis could be the primary event triggering the expression of other profibrotic factors that lead to the development of PD's plaque.

- *Model advantages*
  1. A single injection is adequate to cause a PD plaque formation, with a faster onset of plaque.
  2. This model allows for the investigations for therapeutic agents targeted against these molecular targets, too [8].
- *Model disadvantages*
  1. Cumbersome preparation (Tisseel, Baxter, CA, USA) and difficult injection of viscous substance [8]

7.5.3 Surgical Trauma Model

El-Sakka and coworkers, in 1998, reported prominent inflammatory cellular infiltrates and disorganization of the collagen bundles in the tunica albuginea of rat penis after 8 weeks following the incision and suture repair of the tunica albuginea of the penis [16]. They, by using this animal model, concluded that penile trauma resulted in an early but transient upregulation of TGF-β1 protein expression and histological changes similar to the acute phase of PD [16]. Bivalacqua et al., in 2000, found that needle injection by itself would not cause the histological changes associated with TGF-β1 or surgical injury to the tunica albuginea, and a direct incision of the tunica albuginea was required to replicate the surgical trauma model [11]. Even if interesting, this model is impeded by the potential role of suture material used in the closure of the incised tunica as an inciting event for an acute inflammatory response leading to plaque formation and providing a nidus for a later, chronic inflammatory reaction [8].

- *Model advantages*
  1. Strong PD plaque formation [8]
- *Model disadvantages*
  1. Longer time for plaque formation and fibrotic effect of suture material [8]

7.5.4 Genetic/Spontaneous Model

In 2008, Lucattelli, for the first time, described an animal model of spontaneous PD in tight-skin mice, a C57Bl/6J subline that reproduces with age important features of the human disease (fibrous plaque formation, penile bending and areas of chondroid metaplasia with heterotopic ossification) [17]. This mouse model is the first example of naturally occurring model of PD in laboratory animals. They found an upregulation of hypoxic inducible factor-1 (HIF-1) leading to an increased downstream expression of HIF-1 target genes such as TGF-β1 and iNOS, resulting in the collagen deposition in Tsk penises [17]. The overexpression of HIF-1 and dysregulation in the fibrillin function are likely to result in the development of PD [17].

- *Model advantages*
  1. Strong PD plaque formation [8]
- *Model disadvantages*
  1. Systemic fibrotic process, absence of disease progression after 12 months [8]

7.6 The New Era Model: From Animals to Cell Culture

In 2010, De Young and coworkers, for the first time, investigated the expression of wound healing and fibrosis-associated proteins in primary cell cultures of PD fibroblasts [18]. They showed that primary cell cultures from PD plaque displayed overexpression of several proteins that are established components of fibrosis and wound healing. In particular, they found that statistically significant increases in smooth muscle alpha-actin, beta-catenin, and heat-shock proteins (Hsp47) were identified in cells derived from PD relative to cells derived from normal tunica albuginea tissue [18]. Moreover, they found changes in TGF-β1 receptor and fibronectin in association with altered expression of additional as yet unidentified proteins at 4.7, 8.9, 10.8, 16.8, and 76.8 kDa [18]. They also highlighted that it will be of interest to conduct further studies to see whether these deregulated protein peaks represent potential biological markers of disease progression [18]. Moreover, Del Carlo et al., by using an experimental model in that evaluated matrix metalloproteinases and tissue inhibitors of matrix metalloproteinase from Peyronie's disease plaque tunica removed from patients with stable Peyronie's disease and cell cultures, highlighted the role of the matrix metalloproteinase/tissue inhibitors of metalloproteinase/plasminogen activator inhibitor 1 system and the interplay between the collagenolytic and fibrinolytic pathways and their inhibitors in the pathogenesis of PD [19].

In conclusion, even if the experimental and animal models cannot truly represent the complexity of the human disease, they share some of the histological features that were defined in the human PD plaque [1]:

- Initial inflammation
- Subsequent excessive deposition and disorganization of collagen fibers
- Elastin fragmentation and accumulation of myofibroblasts and profibrotic factors (oxidative stress, PAI-1, TGF b1, and fibrin)

- Potential antifibrotic factors (iNOS)
- Calcification and ossification

Moreover, as suggested by Gonzalez-Cadavid, the experimental and animal models may well serve to extrapolate to PD some promising experimental studies on the molecular pathology of tissue fibrosis in general aimed to counteract this process in such organs as the liver, kidney, lung, or skin, where there is ongoing intense research activity [1].

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Symptoms, Their Physiopathology, and Outpatient Clinical Practice and Diagnosis

8

Carlo Maretti

8.1 Introduction

Peyronie's disease (PD) is a segmentary or diffused fibrosis of the penis' vascular thecae. Some authors have suggested that the onset of microvascular lesions, induced by repeated microtrauma, mostly due to sexual activity but also by acute or mechanical trauma (urological maneuvers, intracavernosal injection, penile injuries), in genetically predisposed subjects, has a primary importance in Peyronie's disease, starting a repair process that hesitates in fibrosis [1]. According to our point of view, the etiological microtraumatic hypothesis justifies also the "a poussée" evolution of Peyronie's disease. Sexual intercourse is potentially traumatic to the penis, causing recurrent microtrauma during erection and inflammatory flare-ups, which eventually revert with fibrous remains. The inelastic, fibrotic plaques can constitute themselves a traumatic factor "ab intrinseco" triggering other microtraumatism in the surrounding tissues; therefore, the erection itself can play a primary pathogenetic role in the aggravation of the disease [2]. The initial stage of PD is thought to last from 6 to 18 months, followed by a chronic phase. The process of formation of the plaques is determined by the interaction of numerous factors, from the macrophage activation to the liberation of cytokines and growth factors that have the purpose to repair the lesioned area [3]. An excessive production or an uncontrolled activity of some of these factors can induce fibrosis [4].

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8.2 Physiopathology

PD is a segmentary or diffused fibrosis characterized by the appearance of inflammatory plaques with formation of palpable plaques in the tunica albuginea of the penis, located mainly in the dorsal side. The plaques can provoke pain during erection and penile bending. One of the characteristic elements of Peyronie's disease is the initial inflammation, located at one or more points of the tunica albuginea, which causes a painful erection, a slow evolution of the scar healing, and a clinical outcome of the penile bending. The duration of the process, the extent of the corpus cavernosum involvement, the degree of deformity, and the possible functional deficit are mostly unpredictable. The structure of the corpora cavernosa is composed of the tunica albuginea, which is made of elastic fibers and two layers of collagen fibers, one outer longitudinal and one inner circular. From the intracavernosal septum connected both dorsally and ventrally with the fibers of the inner circular layer of the albuginea, a fibrous intracavernosal network starts and intersects with the smooth muscle cells of the venous sinuses and arteries.

Normally the corpora cavernosa stretch symmetrically to give a straight axis to the penis during an erection. However, when there are alterations such as a fibrosis of the albuginea or the septum, the process of erection results in a reduced compliance of the corpora cavernosa which is manifested in a narrowing/bending of the penis [5].

Trauma and microtrauma cause a delamination that generally occurs at the junction between the septal filaments of the midline and the circular layers of the dorsal and ventral tunica albuginea (Fig. 8.1). This leads to a microvascular injury with an inflammatory reaction which activates the macrophage with the consequent liberation of cytokines and of the growth factors that have the purpose to repair the lesioned area [6]. The end result of this process is the production of collagen. Since

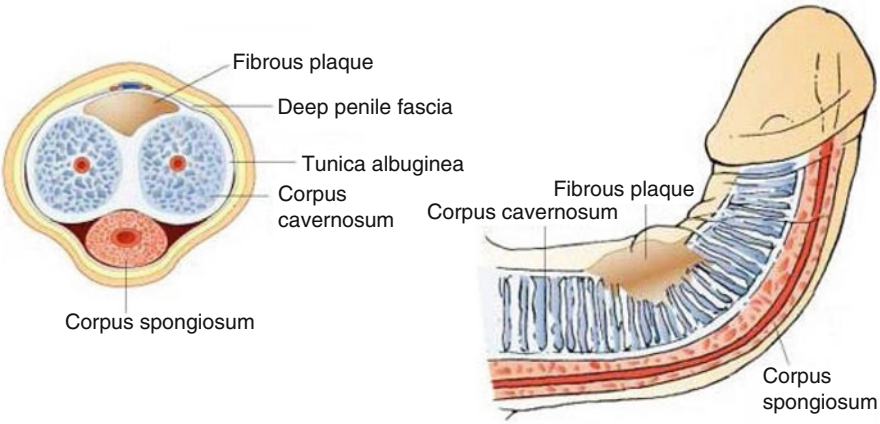

Fig. 8.1 Dorsal penis curvature

the tunica albuginea has a poor vascularization, fibrin and collagen are not removed and the aggregation of the latter leads to the formation of plaques. This causes a reduction in distensibility of the albuginea that can affect the penis length or even its transverse diameter if there is an annular fibrosis, thus compromising the penile functionality (Fig. 8.2). Structural alteration of albuginea elasticity may lead to veno-occlusive mechanisms and decrease the compliance of the intracavernosal septum, with reduced expansion of the tunica albuginea even in healthy sites, not directly affected by the plaque.

The relationship between Peyronie's disease and testosterone levels is still evolving and often confused by conflicting study results.

A retrospective study suggests a possible link between low free testosterone and PD [7]; another study suggests that the presence of T deficiency in patients with PD exaggerates the severity of PD by affecting penile deformity, plaque size, and erectile dysfunction [8]. A prospective study [9] showed that tT, fT, and bT were significantly higher in the healthy controls than in the PD patients and the plaque area was significantly larger in PD patients having bT and fT under the reference range. Furthermore, this study compared intraplaque administration of verapamil between hypogonadal PD patients treated with a placebo and those treated with supplementation of exogenous testosterone. Plaque area and penile curvature significantly improved in the patients using testosterone.

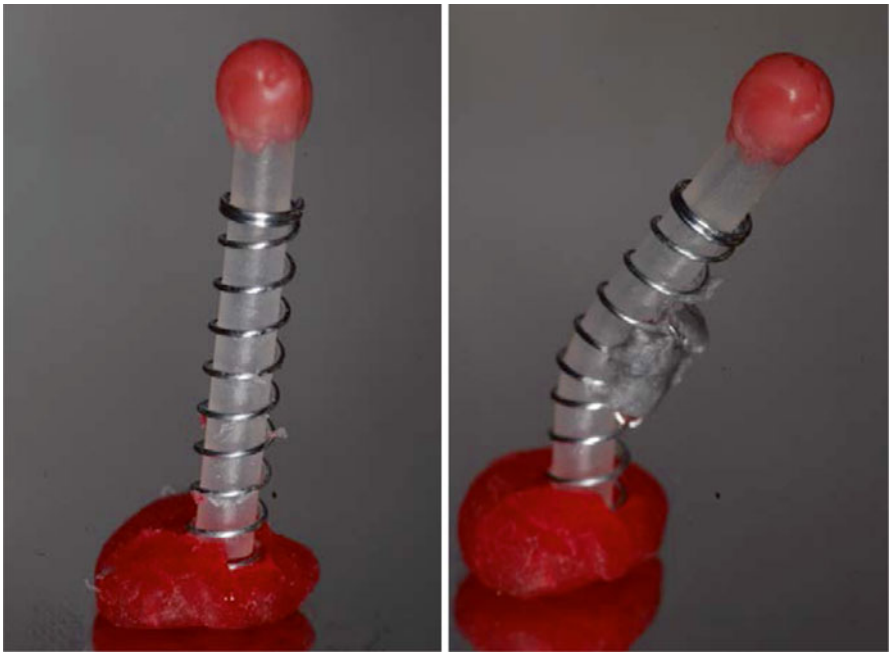

Fig. 8.2 Model representing the mechanic effect of plaque

It is still unclear why the peak onset of PD occurs among men in their 50s if trauma is the precipitant event, as the frequency of sexual intercourse tends to be greater in young men. One possibility is a cumulative effect of repetitive minor injuries to the tunica albuginea over time, and a recent study suggests that it may be due to relatively low serum testosterone levels in older man [8]. Low testosterone levels, by the important association of testosterone with erection, could reduce erectile rigidity and impair tissue response to injury [7, 8].

Results of the effects of testosterone levels and testosterone replacement therapy on markers of inflammation are similarly conflicting. There is growing evidence that proinflammatory cytokine production and the activation of inflammatory signaling cascades are affected by gender and sex steroids, leading to significant gender differences in the ability of some organs to tolerate injury [10–12].

Adequate testosterone levels are required for insulin-like growth factor (IGF) 1 production, and IGF-1 is a wound healing agent [8, 13].

Moreover, transforming growth factor (TGF)-β1 is overexpressed in PD. TGF-β1 stimulates collagen synthesis and induces other profibrotic factors' production [3, 7, 8]. Some evidence demonstrated that testosterone was involved in the downregulation of TGF-β1 production [8], while other studies found that testosterone stimulates the production of transforming growth factor (TGF)-β [14], which can induce a Peyronie's-like condition in the rat [15].

Testosterone and its metabolites, with their anabolic action on the connective tissue, can play an important role in the several phases of inflammation and in the recovery from injuries [16, 17].

In the inflammatory acute phase, interleukin-1 (IL-1) increases the conversion of testosterone in 5 alpha-dihydrotestosterone (DHT) of 1.5 times in inflammatory site, with powerful anabolic effects of DHT on the synthesis of the extracellular matrix of connective tissue and bones [9]. It was demonstrated in vivo that testosterone and its metabolites, estradiol 17-β (E2) and DHT, inhibit the action of cytokines IL-1 and interleukin-6 (IL-6) [18–20] and enhance the angiogenetic response to vascular endothelial growth factor (VEGF) [21], which plays a role in the fibrotic evolution of recovery [22] and acts on the physicochemical constitution of the fundamental substance of connective tissue [23].

There have been few reports showing a direct and organ dependency of androgen for erectile function in the human corpora cavernosa, although there is plenty of evidence demonstrating that low or absent androgens affect a man's ability to have an erection in a sexual situation. Testosterone, in rats, influences the penile production of nitrogen monoxide (NO) [24]. Some data support the hypothesis of testosterone dependence of penile nitric oxide synthesis (NOS) in humans [25]. NO plays various roles in all the phases of the inflammation, it is of fundamental importance in inducing the vasodilatation and seems to regulate the leukocyte recruitment, and moreover, it could influence the vascular permeability [26, 27]. Theoretically, testosterone effects could be considered a key to the disease's progress. This identifies a biological target, which inhibition during some therapeutic phases could prevent microtraumatic injuries and which normal levels could reduce the direct and mediated effects of testosterone and its metabolites on the evolution in fibrosis of the recovery processes.

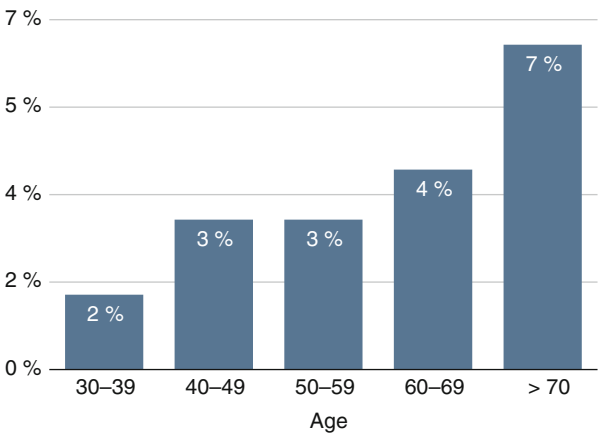

Fig. 8.3 Proportion of men with Peyronie's disease by age group from Sommer et al. [29]

From the epidemiological point of view, it has been estimated that the incidence of the disease is about 1 % in white men and is very low in black men, while no cases have been reported in the Asian people [28]. The incidence rate is higher in men aged between 40 and 60 years even if the disease has been diagnosed in young men. This incidence can be explained also from a histological point of view. Elastic fibers of the tunica albuginea are progressively reduced by the age, giving way to the collagen ones, which can easily be affected by the traumatic phenomena. For a long time, Peyronie's disease was regarded as a rare andrological disorder. In a survey in and around Cologne, Germany, the frequency of Peyronie's disease was determined on the basis of a validated questionnaire [29]. In the total group of 4,423 men investigated, with an average age of 57.4 years, 142 cases of Peyronie's disease were registered. This is equivalent to 3.2 % of the study population. Other investigators found rates as high as 9 %. The condition most commonly develops between the ages of 40 and 60 years but, as the chart below shows, it increases with increasing age (Fig. 8.3).

8.3 Symptoms

The symptoms that often bring the patient to approach the andrologist are pain; formation of a hard, palpable mass; and bending during erection. A study [30] reports as initial symptom penile pain in 27 %, penile curvature in 49 %, and a palpable plaque in 39 % of the patients. The pain occurs in about a third of cases, most frequently during erection, but it almost always resolves spontaneously a few months after the onset of the disease. A tenderness may reappear during the breakthrough of the disease, and this explains the succession of flare-ups [31]. The painful inflammatory phase of the disease results in the release of inflammatory mediators, accentuated when the inflamed tissue is stressed. This mainly happens during induced erections and it is caused by sexual activity or during nocturnal erections, but only occasionally it is liable to affect the sexual act. As it generally precedes the bending/incurvation, it is the presenting symptom of the disease, and therefore it will be a reason for consultation. Most of patients first observe a plaque,

whose appearance is often sudden. The finding of an area of increased thickness on a palpation of the corpora cavernosa is a pathognomonic sign of the disease also in people who do not complain deviation. The most common site is at the backbone of the penis, but the plaques can also form centrally, laterally, or in multiple locations. The subsequent behavior of the plaque is very changeable, and it is not uncommon to increase its volume and consistency for the subsequent deposition of Ca ions. According to the development of the plaque site, an evident penile curvature develops during erection. The disease usually develops in 6–12 months, and during this period, the degree of deformity may change significantly. Decisions about surgery should be postponed until there are clear indications that the disease is stabilized for at least 6 months and that it is present for more than a year. A variable percentage (4–80 %) of men suffering from the disease cannot achieve an erection with complete rigidity: this may be the first symptom of the disease onset, and it can be explained by an involvement of the fibrotic process of the tunica albuginea to the smooth muscle, resulting in a more extensive fibrosis of the corpora cavernosa. Despite these structural correlations with an erectile dysfunction, even psychological factors can interfere with sexual potency. In the study by Gelbard et al. [31], 77 % of PD-affected men complained about psychological effects resulting from the disease. Forty-eight percent of men had persistence of psychological problems even after successful therapy. Insufficient arterial blood supply, venous escape, excessive deformity, pain, and a psychological element associated with PD give rise to performance anxiety. These factors lead to erectile dysfunction. Some studies have reported a 13 % or less rate of spontaneous regression without intervention [31, 32].

8.4 Clinical Practice and Diagnosis

Patient assessment largely depends on his history and on a careful clinical examination. Physical exam should establish the degree and the orientation of the penile curvature and the presence of penile shortening or an hourglass-type indentation. The number and location of plaques must be identified as well. Detection of the plaque on clinical examination is facilitated by stretching the penis with one hand and gently compressing the penile shaft between the fingers and thumb of the other hand. A physical examination of the genitals should include the measurement of the length and girth of the penis when it is on a resting phase and the location and size of the plaque. For diagnostic purposes, it is useful to ask the patient to provide some self-photographs from different angles (top, side, bottom, and front) of the erect penis to confirm both its curvature degree and its ability to achieve full rigidity. The dynamic penile ultrasonography (Fig. 8.4) provides a lot of information on the size, scale, and plaque location and allows to measure any degree of curvature. Doppler ultrasonography with pharmacologic induction of an erection should be performed, and a goniometer can be used to measure bending on sagittal and transverse plane. This evaluation would be useful in evaluating improvement after therapies. The magnitude of penile deformity is a critically important factor in Peyronie's disease, and only half of PD patients accurately assess their penile curvature, with more than

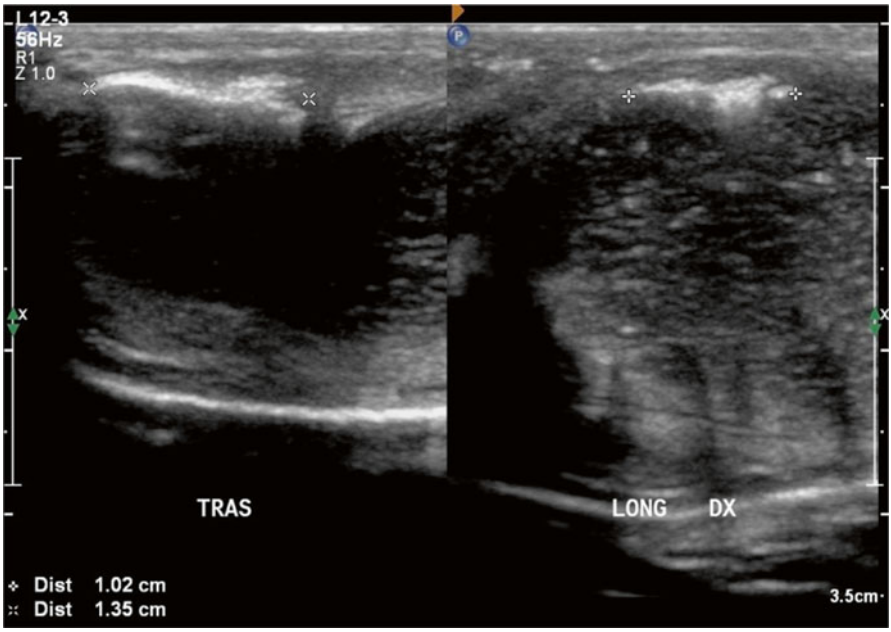

Fig. 8.4 Penile plaque due to Peyronie's disease. Transverse and longitudinal sonogram demonstrates the dimensions of the plaque. Calcified plaque is noted involving the right corpus cavernosum and corpus spongiosum

twice as many patients underestimating it than overestimating it [33]. Assessment performed using intracavernosal injection-assisted erection using a goniometer applied during excellent penile rigidity is mandatory. For this purpose, in our practice we have designed a goniometer drawn on a card (Fig. 8.5). It will be always appropriate to dynamically assess the arterial flow of the penile vascular structures. The measurement of blood flow and vascular integrity determination may be useful in the study of erectile dysfunction often associated to PD. The venous insufficiency seems to be a consequence of fibrosis which limits the arterial flow and determines an inability of the total extension of the tunica albuginea, resulting in a decreased compression of the perforating veins afferent to the dorsal vein (Fig. 8.5). X-rays and CT are able to detect calcifications of Peyronie's plaques and to determine the degree of plaque calcification [34]. Noncalcified plaques, however, cannot be shown accurately. The limited information gained by these methods does not support the extent of ionizing radiation used for this purpose [35]. MRI is at least as sensitive as ultrasonography to determine the extent of plaque formation [36]. Nevertheless, MRI is an expensive imaging modality and is not commonly used in our clinical practice to evaluate patients with PD.

Other possible causes of penile bending and induration must be considered. The differential diagnoses include congenital curvature of the penis, chordee with or without hypospadia, dorsal vein thrombosis [37], albugineal scar, and cavernosal fibrosis secondary to local trauma, chronic inflammation, scleroderma [38], and benign or malignant primary or secondary tumors. A rare condition is epithelioid

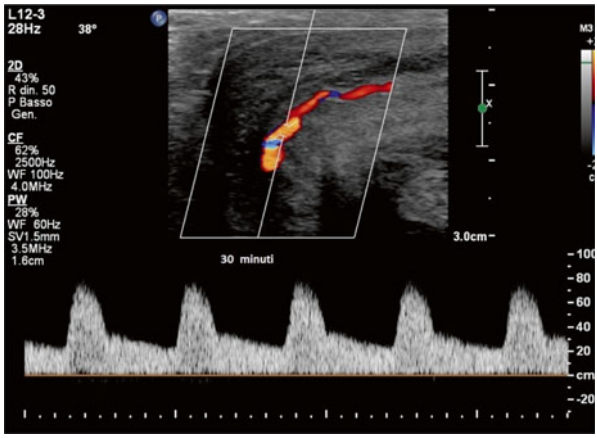

Fig. 8.5 Venous incompetence in erectile dysfunction. Peak systolic velocity and end diastolic velocity were measured in the cavernous arteries over 30 min. The end diastolic velocity >5 cm/s is indicative of venous leakage

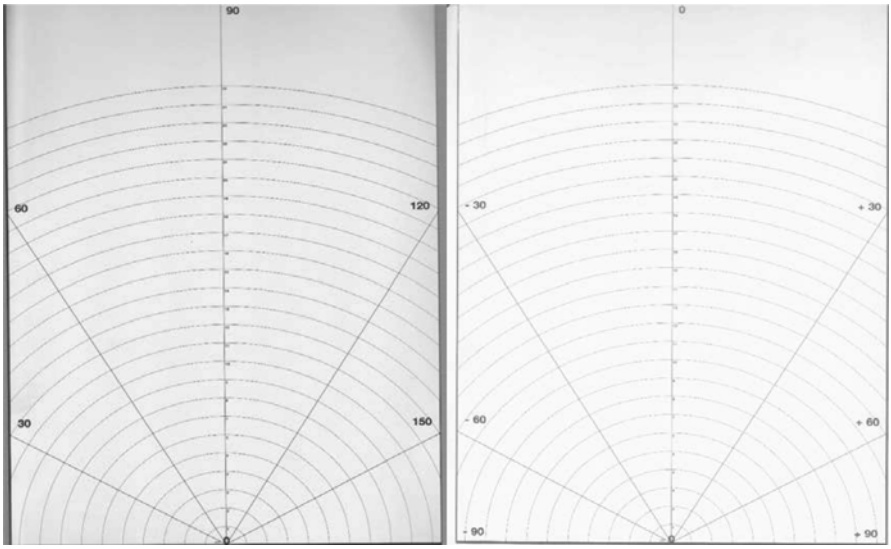

Fig. 8.6 Bending can be measured with a goniometer graduated from 0 to 180° for the midsagittal plane and from −90° to +90° for the transverse plane

sarcoma of the penis, a slowly growing mesenchymal neoplasm, which may manifest as focal induration and can mimic PD [39, 40]. Isolated fibrosis of the penile septum [41] and ventral curvature secondary to fibrosis and scarring of the corpus spongiosum should be considered, as it can be the result of urethral instrumentation [42].

For many patients, the impact of PD is both functional and psychological. Both aspects should be evaluated and treated in patients. Interventions aimed at education, coping, relationship distress, and sex therapy may significantly improve patient quality of life. The physical pain, emotional distress and isolation, and partner and relationship discord that may be present require great attention [43] (Fig. 8.6).

Conclusions

Peyronie's disease is a condition involving middle-aged men and probably resulting from penile trauma. The injury causes an inflammation in the tunica, and ultimately scarring and penile curvature develop. The normal elastic tissue of the tunica is replaced by scar tissue. The penile plaque is not elastic and will not stretch with erection. The side that does not stretch results in penile curvature to the side of the scar. One-third of men with Peyronie's disease have painful erections. Most patients with early-stage disease can continue to function sexually with the curvature in the penis. Others with a severe penile deformity will have difficulty in sexual intercourse. Diagnosis is based on medical and sexual histories; physical examination includes assessment of palpable nodules and penile length. Curvature should be documented by self-photograph and measured with a goniometer after pharmacologically induced erection. Ultrasonography shows high sensitivity in detecting calcified plaques, and even noncalcified plaques of fibrosis can be detected. Exact measurement of plaque size makes it useful for following up patients. Sonography and the color duplex technique is the proper assessment of the penile vessel status, as erectile dysfunction occurs in about one-third of the patients. An important step for improving our understanding of PD would be to determine the hormone profile associated with PD and with its severity, not only regarding testosterone levels but investigating relationships with gonadotropins, E2, DHT, and prolactin for a complete hormonal assessment.

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Congenital and Acquired Penile Curvature: Relationships and Differences

9

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9.1 Introduction

Penile curvature can occur congenitally (CPC) by disproportional growth of the corpora cavernosa, frequently leading to a ventral curvature, or can be acquired (APC) by trauma to the corpora cavernosa or, generally, by Peyronie's disease (PD).

Patients with penile curvature may complain of painful erection, discomfort during intercourse, difficult or impossible penetration, and erectile dysfunction (ED), either organic or secondary to the psychological troubles caused by the anatomical condition.

The prevalence rates of PD range from 3.2 % in a German sample to 8.9 % in a sample of American men undergoing prostate cancer screening [1, 2].

Congenital penile curvature is also not uncommon, and its prevalence has been reported to be 0.4–6 per thousand [3]. As this condition requires erections for its diagnosis, unlike other congenital malformations, it is not evident at birth or in childhood, and often it is underdiagnosed [4].

Surgery remains the mainstay of treatment for patients with congenital penile curvature and Peyronie's disease (evident ≥1 year and with a stable deformity for months) not responsive to medical treatment [5].

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The two major types of repair may be considered for both CPC and PD patients: penile shortening and penile lengthening procedures [6]. Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimize penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities.

Finally, in patients with Peyronie's disease and erectile dysfunction not responding to medical treatments, the surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [7]. Choosing the most appropriate surgical intervention is based on penile length assessment, curvature severity, and erectile function status [8]. Obviously, patient expectations from surgery must also be included in the preoperative assessment.

Nevertheless, it is mandatory to take a careful medical and sexual history and to carry out a complete physical exam, including objective measurements of penile curvature at maximal rigidity, as it has been well documented that many patients tend to overestimate the degree of their curvature [9].

Until now, the correspondence between patients' opinion of the degree of penile curvature and objective measures is inadequately studied.

The primary objective of the current study was to correlate patient estimates of the degree of penile angulation with objective measures performed by trained specialists.

The secondary objective was to study if there are any differences in the real and perceived magnitude of curvature among patients affected by acquired penile curvature (APC) versus patients with congenital penile curvature (CPC).

9.2 Subjects and Methods

9.2.1 Study Population

Patients presenting to our academic urology institution with established Peyronie's disease (PD), congenital penile curvature, and/or penile plaques were included in our study.

We collected patient data prospectively between January 2013 and September 2014.

A comprehensive medical and sexual history, physical examination, and focused laboratory and radiological (Doppler ultrasound for patients with PD and penile plaque) investigations were performed. The specific data collected included patient demographics, medical comorbidities, and medication exposure.

Erectile function was objectively evaluated by the International Index of Erectile Function (IIEF-5) [10], and depression-related symptoms were assessed by a 21-question multiple-choice self-report inventory questionnaire [11].

As part of the baseline office assessment, all patients were asked to provide a drawing of their penis in erection, true superior and true lateral view. An objective measurement of curvature direction and angle was performed using two intersecting

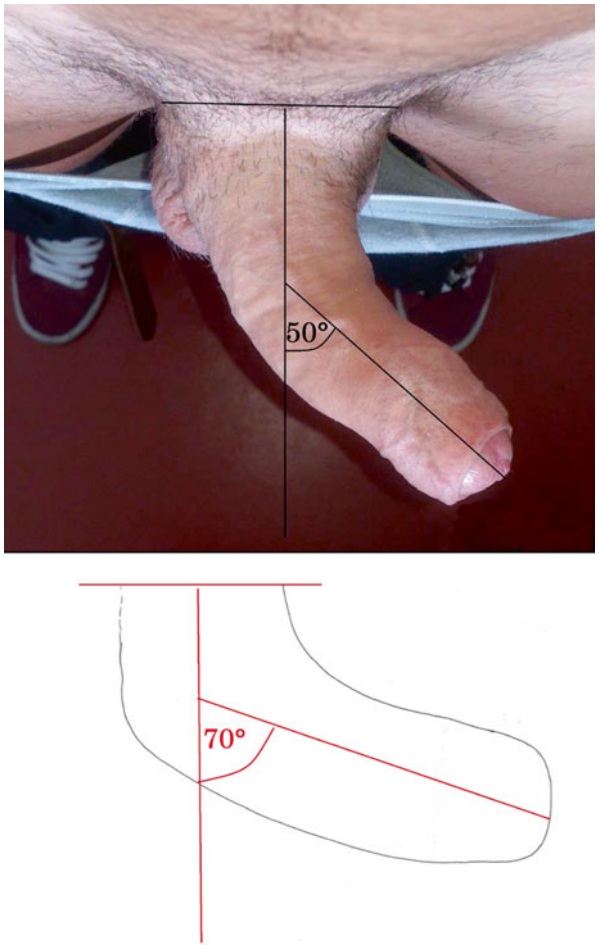


Fig. 9.1 Objective measurement of the degree of penile curvature was performed on standardized photographs and on the drawing of the same penis during erection using two intersecting lines

lines (A and B) through the center of the distal and proximal penile shaft. These measurements were recorded by the physician and placed in the medical record.

9.2.2 Objective Assessment of Penile Curvature

Standardized (true superior and true lateral) photographs of the penis during peak erection induced with intracavernosal injection of 10 μg of PGE (Caverject). Peak erection was defined as the patient's impression of maximal achievable penile rigidity.

Using a ruler and starting at the base of the penis (proximal shaft), a straight line was drawn through the absolute center of the penile shaft (Line A). A second line (Line B) was drawn along the angle of curve through the center of the penis starting at the penile tip (distal shaft) that intersected with Line A. The degree of curvature was determined by protractor measurements of the angle between the two intersecting lines (Fig. 9.1) [12].

The physician measured the magnitude of the curvature and recorded the degree of curvature.

Patients who had curvature with significant associated deformities (hourglass, indentations) were excluded. Patients with curves in multiple planes were classified according to the direction of the dominant deviation.

9.2.3 Concordance Assessment

The patient's assessment of his curvature was considered accurate if it fell within ± 5° of the range that represented the physician's estimate.

9.2.4 Statistical Analysis

Descriptive statistics and percentages were used to describe the patient characteristics and photographs – patient concordance. All statistical analyses were conducted with SPSS for Windows (SPSS 16, SPSS Inc., Chicago, IL, USA). The Pearson coefficient was obtained to evaluate the correlation between the patient estimates and objective measures of penile angulation. Chi-squared statistics were used to evaluate significant proportion/frequency differences among the subjects. A multivariate analysis was made to assess the correlation with penile curvature and erectile dysfunction (for IIEF < 21 pts.) and between the curvature degrees and curvature overestimation.

9.3 Results

9.3.1 Patient Characteristics and Descriptive Analysis

The sample consisted of 88 men, 69 affected by acquired penile curvature (APC) and 19 affected by congenital penile curvature (CPC). Patients' characteristics were resumed in Tables 9.1 and 9.2.

In patients with Peyronie's disease, the median of the length of disease was 10 months. The median period between the onset of the disease and the first clinical evaluation was 4 months. Significant differences regarding BDI-II score were not observed. No statistical difference was found in IIEF score in the two groups. Eighteen patients (21 %) had biplanar curvature, and these subjects were classified according to the direction of the dominant deviation.

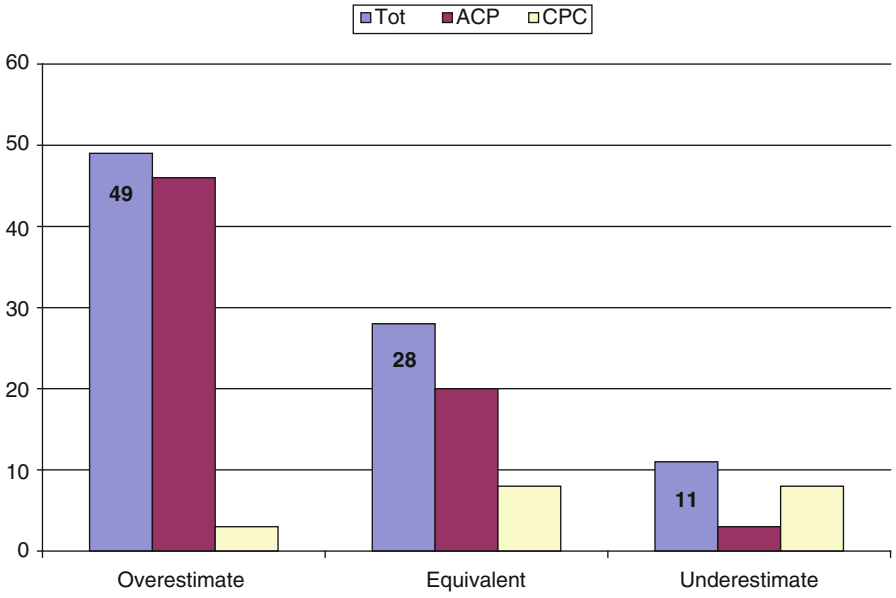
Patients' evaluation frequencies were resumed in Graphic 9.1. Sixty patients (80 %) did not assess correctly their penile curvature: 49 (81.6 %) in APC group and 11 (18.4 %) in CPC. In the APC group, 46 patients (93.87 %) overestimated their curvature and three patients (6.13 %) underestimated their curvature. In the CPC group, eight patients (72.72 %) underestimated their curvature and three patients overestimated their curvature (27.28 %).

Table 9.1 Patients' characteristics

	N of patients (%)	Age, median (SD)	Physician measures, median (SD)	Patient measures, median (SD)	Δ of measures	N of ventral curvatures (%)	N of lateral curvatures (%)	N of dorsal curvatures (%)
Acquired penile curvature	69 (*78.4*)	54 (*11.01*)	45° (*17.77*)	60° (*21.61*)	+15°	1 (*1.4*)	22 (*31.9*)	46 (*66.7*)
Congenital penile curvature	19 (*21.6*)	26 (*11.73*)	45° (*24.90*)	35° (*20.02*)	−10°	13 (*68.4*)	5 (*26.3*)	1 (*5.3*)

Table 9.2 Other clinical characteristics of patients with acquired penile curvature

Pain	Flaccid	12 %
	Erection	37 %
	Coital	45 %
Inability to penetrate		46 %
Dyspareunia		25.4 %
Anxiety/stress		71.6 %
Comorbidities		
Hypertension		27 %
Diabetes		18 %
Dupuytren		16.4 %
Marital status		
Married		80 %



Graphic 9.1 Frequencies of curvature estimation

9.3.2 Univariate Analysis

Mean patient estimates of baseline penile curvature was 45.97 (SD 19.4) degrees. The mean degree of penile angulation obtained by objective measurement was 55.4° (SD 22.2°) and differed significantly from patient estimates ($p < 0.05$). The mean curvature on patient self-report and physician assessment was 59.06° versus 45.43°, respectively, in APC group and 42.37° versus 47.89 in CPC group. The mean difference between the two measurements was +13.48 (SD 16.2) degrees in

APC group and −5.53 (SD 11.5) degrees in CPC group. This data was statistically significant ($p < 0.01$).

No differences were found between APC and CPC by the degree of curvature according to the Kelami classification.

Differences between the patients' estimated curvature and objective measures were significant when stratified by the direction for ventral and dorsal curvatures ($p < 0.05$), not for the lateral curvatures.

Differences between the patients' estimated curvature and medical therapy were not significant.

9.3.3 Multivariable Analysis

Logistic regression predicting physician-patient concordance was tested using all the variables.

Multivariate analysis revealed degrees of curvature ($p = 0.018$) and IIEF score ($p = 0.023$ for IIEF < 21) as independent predictors for patient's overestimation.

9.4 Discussion

In this study, we found that:

1. Only 32 % of patients (28/88) affected by penile angulation accurately assess their penile curvature.
2. The results are very different in patients with acquired curvature than those with congenital curvature.
3. For the 60 patients (68 %) who did not accurately assess their curvature, APC patients generally overestimated than underestimated their curvature versus CPC patients (67 % vs. 16 %; $p < 0.005$). On the contrary, CPC patients collectively underestimated their curvature compared to APC (42 % vs. 4 %; $p < 0.005$).
4. Multivariate analysis revealed the grade of curvature and ED with IIEF < 22 as independent predictors of curvature overestimation.

Since there is neither an established nor effective medical therapy for managing PD or CPC, surgery is usually considered for patients who have significant curvature that impairs sexual intercourse and share the same principles in both pathologies.

Although congenital penile curvature and Peyronie's disease have a pathophysiology and natural history that are completely different, the degree of curvature is the most important aspect in both pathologies since greater magnitude can make penetration difficult or impossible for the patient and painful for his partner.

The precise evaluation of penile curvature is the crucial point in the management of patients affected by PD or CPC.

The degree of penile curvature has important effects on patient counseling regarding disease severity. Moreover, accurate assessment of penile deformity prior to surgery allows optimization of deformity correction. As a matter of fact, the surgical approach is determined significantly by the degree of curvature; other factors are the presence of hinge effect and of concurrent ED [13, 14].

It is generally recognized that plication procedures, for example, are best utilized for men with mild deformity, while larger curvatures are amenable to correction using plaque incision and grafting or penile prosthetic approaches [15].

Furthermore, the degree of angulation is also a primary end point in the assessment of the results of any intervention in PD and CPC patients.

It is commonly considered that the gold standard means of curvature measurement is by intracavernosal injection (ICI) with degree of angulation determined while erect. Alternatively, curvature may be assessed by at-home photography (AHP) during the erect state or by the use of a vacuum erection device (VED) to induce an erection [12].

In English literature, the issue of accurate assessment of penile curvature magnitude is poorly studied, and there is variation in how penile curvature is assessed, including the use of patient self-reports, photography, "eyeball" measurements, protractors and rulers, and goniometers [15–17].

Ohebshalom [12], examining the concordance between these three most commonly used methods of penile curvature measurement, found that measurement of penile curvature by either VED or AHP significantly underestimated the degree of angulation compared with the deformity assessment after ICI, with an escalating significance with increasing degree of curvature and increasing degree of ED.

Given that there is no currently accepted standard approach to the evaluation of the patient with penile deformity nor any previously published analysis of existing approaches, a survey was performed by Levine in 2003 [14]. The results of this survey revealed several important factors. Deformity was measured objectively with respect to curvature in only 38 % of articles and specifically by "eyeball estimate" in 7 %, photograph in 7 %, protractor in 6 %, and unspecified in 18 %.

More recently in a similar study, Müller reviewed 26 PD intervention studies published over a 15-year period: of the 23 studies in which deformity assessment was reported, he found that 78 % assessed curvature by ICI, while 9 % used vacuum devices. Sixty-one percent used photography to document the curvature, and of these, 36 % relied on a photograph taken by the patient himself, and 13 % used the photography as the only form of deformity assessment [18].

Although this type of survey is incomplete and presents several biases, the results are definitely representative of the problem that we face in terms of making sense of the available published literature.

The question remains as to how penile curvature must be documented particularly in patients who need to be operated and for men entering clinical trials.

However, determining the best of these three methods of deformity assessment is beyond the scope of this analysis; conversely, the primary objective of our study was to correlate patient estimates of the degree of penile angulation with objective measures performed by trained specialists. In our opinion, this is a key issue, because,

even nowadays, many clinicians and published studies have relied on patient self-assessment of penile curvature, despite clinical experience suggesting that patient and in-office clinician assessments of curvature are discordant.

It is undoubtedly useful to ask the patient to estimate the degree and direction of erect penile curvature. However, it has been demonstrated that only 20 % of PD patients accurately report the degree of curvature with 54 % overestimating and 26 % underestimating curvature with an average difference of 20 grades, which is why preoperative objective measures of erect deformity are necessary in order to accurately counsel patients, recommend appropriate treatment, and objectively evaluate outcomes [9].

Very recently, Matsushita et al. [19] studied the concordance between patient and physician assessment of the magnitude of Peyronie's disease curvature in 192 patients who presented for evaluation of Peyronie's disease-associated penile curvature. Interestingly, they found opposite results compared to the previous report: no more than 16 % of patients overestimated their curvature, while 35 % underestimated it and only 49 % correctly assessed their deformity. They explained this finding based on patients getting "peak" erections (with resultant "peak" curvature) on ICI that they did not experience at home.

Moreover, in their study, they found that men with stronger erections were more likely to assess their curvature accurately.

In accordance with the previous report, in our study we found significant differences between patient estimates and objective measurements of penile angulation performed by trained experts, with only 32 % of patients correctly assessing their curvature. Collectively, patients tended to overestimate (56 %) their degree of curvature. This was not influenced by disease severity according to the Kelami classification. On the contrary, differences between patient estimates and objective measures were significant when stratified by the direction for ventral and dorsal curvatures, not for the lateral curvatures. Moreover, multivariate analysis revealed degrees of curvature ($p = 0.018$) and IIEF score ($p = 0.023$ for IIEF < 21) as independent predictors for patient's overestimation.

The secondary objective was to study if there are any differences in the real and perceived magnitude of curvature among patients affected by acquired penile curvature (APC) versus patients with congenital penile curvature (CPC). To the best of our knowledge, this item was never studied before in English literature.

The psychological impact of the penile deformity in men with congenital penile curvature is currently unknown, and no data are available in literature, but can be presumed to have at least as great a negative effect on QOL as it does in PD patients.

As a matter of fact, PD is well recognized as a cause of distress and depression, as well as ED. Men with PD may have poor body image leading to mood disturbances, low self-esteem, and emotional distress. They report a feeling of loss of physical attractiveness and virility, as well as fear of partner sexual dissatisfaction [20, 21].

Our results seem to show that patients with acquired curvature significantly overestimate their curvature than patients with congenital curvature which, on the contrary, generally underestimate it.

The reason of this difference is not known and is not the object of this study.

It is likely that, if the deformity appears after the patient's self-image has already been well defined, the perception of self-reported magnitude is worse. Otherwise, a patient with a congenital curvature made an eye to his penis during growth, and his curvature was self-recognized from his early teens with the development of sexual self-awareness, showing minor psychological implication.

In our opinion, if these results will be confirmed in the next future by randomized controlled trials with a larger number of patients, the counseling and the management of the patient with congenital curvature could change significantly.

Conclusion

Our results confirm that only the minority of patients with curvature of the penis accurately assessed their deformity. Patients with APC have a propensity to overestimate their degree of penile curvature, while CPC patients tend to underestimate it.

Subjective reporting by the patient allows an estimate of curvature which is important to document, but there can be a significant discrepancy between the patient's estimate and objective measures of curvature.

Objective calculation of penile angulation is mandatory to correctly counsel patients concerning disease evolution and suggest proper treatment and objectively assess outcomes following therapy.

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Psychological Aspects of Peyronie's Disease

10

Giorgio Cavallini

Patients live their Peyronie's disease (PD) as an embarrassing disorder. They often refer about a variety of related psychological effects: reduced quality of life, discomfort, depression, low self-esteem, and emotional distress. These psychological attitudes are mostly due to the change of their physical appearance and self-image induced by PD penile deformity. These factors have been reported to reduce the quality and frequency of sexual relationships, reduce libido and intimacy, and cause social and personal difficulties for relationships [2, 4]. These data make PD patients strong candidates for psychotherapy.

Farrel [2] documented the effect of PD on the psychosocial status of 92 men with the Center for Epidemiological Studies Depression (CES-D) scale for evaluation of depression and the SF-36 for quality of life. Eighty-eight percent of the patients had a partner. Forty-eight percent were classified as depressed on the CES-D (26 % moderate, 22 % severe). The severity of depression does not have any relationship with the time between diagnosis and disease onset. These patients obviously displayed a lower Mental Health subscale (MHS) score than the general male population standardized mean of 50. These data mean that 48 % of men with PD have clinically meaningful depression that would warrant medical evaluation.

An attempt to identify risk factors associated with psychosocial difficulties in men with PD has been recently performed. The analysis of the data indicated that emotional difficulties (OR 6.9, $P<0.001$) and ability to have intercourse (OR 0.4, $P=0.004$) were independently associated with relationship problems. Relationship problems (OR 8.0, $P<0.001$) and loss of penile length (OR 2.7, $P=0.02$) were significant independent predictors of emotional problems after adjustment for the ability to maintain erections, low libido, and penile pain. These data mean that medical

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and surgical therapies may enhance quality of life through their ability to improve sexual function [5].

PD patients are concerned about six key areas: (1) physical appearance, (2) sexual self-image, (3) loss of sexual confidence and feelings of attractiveness, (4) sexual function and performance, (5) performance anxiety and partner's sexual dissatisfaction, and (6) social stigmatization and isolation [4].

The surgical straightening of congenital penile curvature improved intromission comfort and penile features, but it failed to improve interpersonal relationships or psychogenic ED [1]. Thus, it may be argued that personality traits are involved as well in depressive episodes after deformity onset in the course of PD.

The depressive aspects of PD patients might explain their pessimistic evaluation of penile curvature (see the Chap. 9).

These data indicate the need of an improved awareness and education about the psychological consequences and treatment options for physicians treating PD. The presence of psychologists inside the team treating PD is welcome for patients' and their partners' mental health [3].

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Imaging in Peyronie's Disease

11

Marco Bitelli

Diagnostic imaging, especially ultrasound (US) scanning, is a mainstay in the evaluation and follow-up of Peyronie's disease (PD) or induratio penis plastica.

Diagnostic imaging for PD is substantially based on US – mainly penile ultrasound and colour Doppler sonography – and examination with soft x-rays. Magnetic resonance imaging (MRI) and computed tomography (CT) have a minor role. A further recently introduced imaging modality, sonoelastography (SEL), is based on the different elasticity of healthy and pathological tissue.

US imaging is not considered as a first-line examination by EAU 2010 guidelines (level of evidence 3, grade of recommendation C) [1], which in fact mentions only home (self) photograph of a natural erection as a means to evaluate PD. However, in clinical practice, the vast majority of urologists, andrologists and radiologists assess PD plaques by ultrasound due to its high diagnostic accuracy, reproducibility and cost-effectiveness.

US imaging is also a key approach to evaluate disease progression through the various stages [2].

Colour/power Doppler imaging provides objective data to assess vascular erectile function as well as the possible influence of tunica albuginea fibrosis on the veno-occlusive mechanism – a common problem in subjects with PD. It also provides valuable information to assess the scope for surgical management [3, 4], since the arising of vascular impairment concomitant with or subsequent to PD onset may respond to a combined surgical approach including penile curvature correction with a dermal patch and implantation of a penile prosthesis [3].

The accuracy, hence the diagnostic performance, of US is substantially affected by two factors, operator skill and equipment. As in other US diagnostic modalities, the procedure is heavily operator-dependent with quite a steep learning curve. The

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scanner should be a last generation machine endowed with the most recent image processing algorithms and a 5–12 MHz linear array transducer.

11.1 Baseline Ultrasound Scanning (B-Mode)

It involves examination of all the anatomical structures of the penis (corpora cavernosa, tunica albuginea, Buck's fascia, intercavernous septum, corpus spongiosum and dorsal neurovascular bundle) with reporting of any abnormalities, particularly fibrous plaques.

Plaques may affect the dorsal, ventral and lateral tunica albuginea or the septum, with or without involvement of adjacent cavernous tissue.

The most frequent PD findings on B-mode ultrasound include:

- *Hyperechoic lesion without posterior acoustic shadowing*
  The intact tunica albuginea is depicted as a thin, predominantly hyperechoic line with variable echogenicity enveloping the corpora cavernosa bilaterally. Lesions appear as thickened and/or abnormal hyperechoic areas of the tunica or septum without posterior shadowing. Such findings account for 40–60 % of patients with early disease (inflammatory stage) [5, 6].
- *Hyperechoic lesion*(*s*) *with posterior acoustic shadowing*
  This is the most common US presentation.
  The lesion is depicted as a hyperechoic thickening of the tunica or septum with variable attenuation (posterior acoustic shadowing) due to plaque calcification [7], and is typical of stable disease (Figs. 11.1 and 11.2).
  These two presentations account for the majority of PD cases. Some patients however demonstrate less common findings that are often difficult to interpret.
  US examination approaches 100 % sensitivity in detecting and measuring calcified plaques.

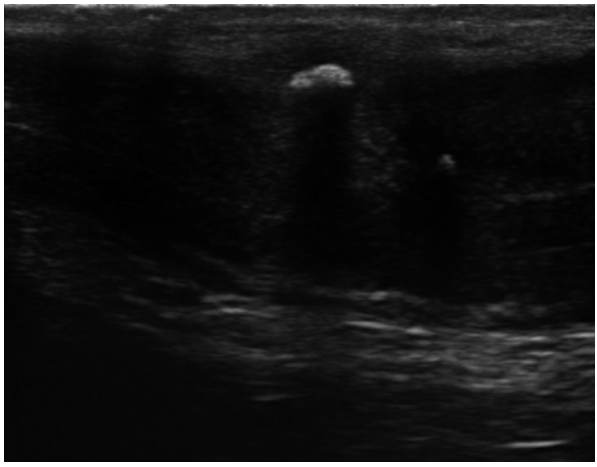

Fig. 11.1 Hyperechoic lesion with posterior acoustic shadowing

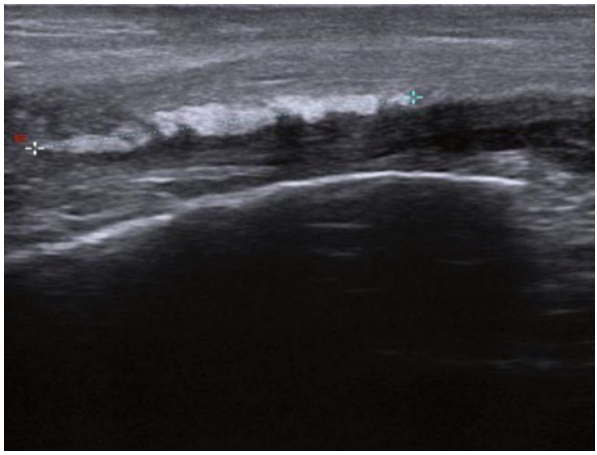

Fig. 11.2 Hyperechoic lesion of septum

- *Hypoechoic/isoechoic lesions*
  Plaques occasionally present as hypoechoic/isoechoic lesions with focal thickening around the corpora cavernosa [8]. Such lesions are typical of early disease, which is characterized by mild fibrosis, strong interstitial oedema [5] and retraction of the tunica albuginea at the level of the lesion, all of which result in penile curvature. In patients receiving stimulation with prostaglandin E_1 (PGE_1), US imaging depicts the actual extent of the lesion, which is often difficult to assess in the flaccid penis, and can sometimes document hyperechoic lesions that are detectable only under pharmacostimulation.
- *Focal defects of the tunica albuginea*
  Focal defects of the tunica associated with a thickened posterior area are found infrequently, except in large series. The surrounding tunica may not be thickened, but it may have an abnormal undulating appearance (Fig. 11.3).
- "*Hourglass*" *deformity*
  It is a hypoechoic or hyperechoic lesion of the tunica that involves its whole circumference, especially its proximal portion. Pharmacostimulation results in an hourglass shape of the shaft portion affected by fibrosis. It is not necessarily associated with a calcified plaque and may merely be the result of a circular lesion of the tunica [8].

Negative US findings in presence of a clinically palpable plaque are frequently reported, but have not been specifically investigated.

11.1.1 Colour Doppler Penile Ultrasonography

Colour Doppler Penile ultrasonography is another useful US modality in the workup of suspected PD. It provides information on lesion morphology, structure and size as well as on vascular erectile function. The accuracy of US imaging, hence its

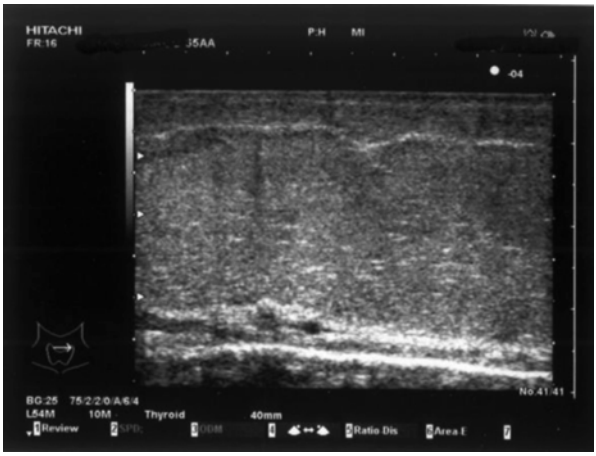

Fig. 11.3 Focal albuginea defect

diagnostic performance, depends on operator skill and equipment type. As in other US diagnostic modalities, there is a fairly steep learning curve. The scanner should be a last generation machine endowed with the most recent image processing algorithms and a 5–12 MHz linear array transducer.

Before beginning the examination with the patient in supine position, accurate palpation is important since it allows to locate the plaque (or plaques in multifocal disease), assess its consistency and make a rough evaluation of its size to form an idea of what will be depicted on the screen. Longitudinal and transverse scans need to be obtained along the ventral and dorsal aspects of the penis, including the urethral bulb and the crura by passing the transducer under the scrotum and along the perineum. All penile structures need to be assessed, including the tunica albuginea, corpora cavernosa, corpus spongiosum and glans, before evaluating the plaque(s). The examination consists of two phases, baseline and dynamic. The *baseline phase* involves investigation of tunica thickening (diffuse or localized); identification of plaque number, site and size; and assessment of any septum involvement. Longitudinal and transverse diameter and thickness are then measured, and plaque volume is calculated, usually automatically by the scanner. Any calcifications need to be identified, counted and individually measured for size. Plaque size and calcification are the main parameters to assess response to therapy.

The *dynamic phase* begins with intracavernosal injection of PGE_1 (usual dose 2.5/10 μcg). Spectral Doppler is essential to measure flow velocity at the level of the cavernous arteries and is commonly evaluated from the penile base, where the Doppler angle ensures more accurate measurement. Colour Doppler examination allows measuring peak systolic velocity (PSV) and end-diastolic velocity (EDV), which enable (calculation of the resistance index RI) detection of normal helicine arteries (Fig. 11.4) and any cavernosum-spongiosum or cavernosum-superficial shunting. Such measurements are performed at precise intervals, usually 5, 15 and 30 min from PGE_1 injection.

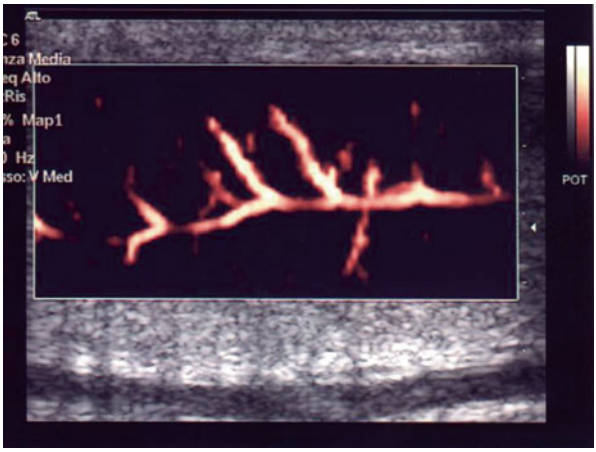

Fig. 11.4 Normal helicine arteries

The erection induced in the dynamic phase also enables a photograph to be taken and calculation of the so-called angle of curvature, another useful measure for follow-up evaluation.

The subsequent morphological colour/power Doppler study of the microcirculation provides information on any associated vascular deficits, especially in patients with vasculopathy, diabetes or cardiovascular risk factors, where the three branches of the helicine arteries are difficult to depict if their angle is <90°, a finding that in turn is responsible for erectile dysfunction due to predominantly distal arterial disease.

The dynamic phase also depicts any site-specific venous leakage around the plaques – i.e. venous outflow on the edges of the hyperechoic lesion – which develops about 12 months from disease onset in patients with erectile dysfunction and a veno-occlusive defect documented by Doppler ultrasonography. These findings are seen in 12–20 % of patients and are responsible for secondary venous outflow [9] (Fig. 11.5).

In some patients with severe PD, persistent cavernosum-spongiosum shunts seen close to the plaques are associated with a higher PSV and a lower RI compared with the other cavernosum-spongiosum shunts, supporting the hypothesis that blood loss may also occur through these vessels [10].

According to some studies, Doppler examination can detect hyperperfusion around the plaques as a sign of inflammation in the active disease stage, whereas the absence of colour signal around them should be considered as a sign of disease stabilization [11, 12].

The most common vascular abnormality seen in PD patients is impaired veno-occlusive function. In particular, they present an increased incidence of venous leakage than their peers [13, 14] (Fig. 11.6).

Whereas in normal erection the venules draining the corpora cavernosa are passively compressed by the expanded cavernosal tissue and the tunica albuginea, in PD patients the reduced elasticity of the tunica albuginea limits such stretching,

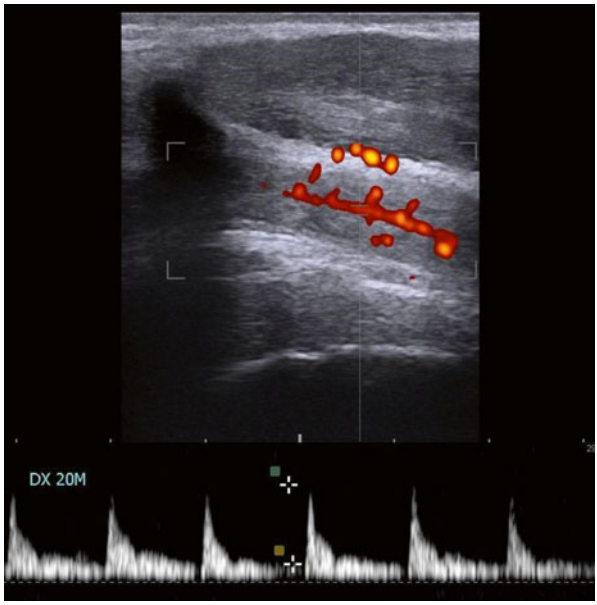

Fig. 11.5 Venogenic erectile dysfunction in PD

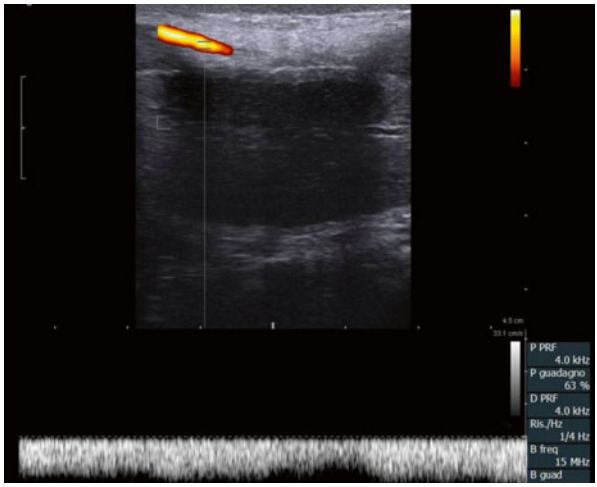

Fig. 11.6 Site-specific venous leakage close to plaque

preventing vein compression. As a consequence, Doppler flowmetry shows high diastolic velocity throughout the examination, with lower than normal RI values [15].

The severity of the veno-occlusive impairment is proportional to plaque extension and disease stage.

In patients with diseased deep cavernosal tissue due to plaque extension and severity, or where the severe retraction involves its compression, the course of the cavernosal artery is affected, resulting in upstream perfusion deficit and signs of

secondary arteriogenic deficiency. In such patients, the reduced systolic values are accompanied by arterial entrapment on morphological colour/power Doppler.

11.1.2 Penile Radiography with Soft X-Rays

This technique exploits mammography units and applies x-rays with a wavelength >0.1 nm, which are especially suited to the examination of tissues like those of the penis (Fig. 11.7). The approach is useful especially because of its ability to differentiate calcifications from the surrounding fibrotic tissue, which on US share a similar echogenicity, affording more accurate measurement.

11.1.3 Penile Sonoelastography

Healthy and diseased human tissues are characterized by appreciable differences in their elastic properties. Indeed, some conditions affecting tissues, such as tumours, induce changes that reduce soft tissue elasticity and mobility. This finding has inspired the notion that tissue elasticity may be assessed in vivo using US waves, i.e. US imaging, at least to examine the organs or glands lying close to the surface.

The method evaluates the change in radiofrequency pulses in a primary structure before and after manual compression (freehand SEL). The elastogram thus obtained is superimposed on the B-mode image as an overlay. The different elasticity of scanned tissues is shown in the form of a colour scale that ranges from red (elastic) to green (intermediate) and blue (stiff).

The examination lasts a few minutes and is usually the final scan after conventional US imaging has depicted suspicious nodules. Very few studies have used SEL to study penile conditions, and most of them have examined PD plaques.

Fig. 11.7 Penile radiography with soft x-rays. Evidence of multiple penile calcifications

In PD patients, the fibrotic areas are blue. SEL is valuable in that cases to document plaques in the septum, especially plaques that cannot be detected by B-mode US [16, 17]. In addition, SEL can provide useful data, especially in early disease, by depicting changes in tissue inflammation around plaques [18].

11.2 Penile CT

CT examination can detect calcified PD plaques and determine their degree of calcification. However, it does not accurately depict non-calcified plaques. The information that is obtained from CT scanning does not justify its cost; therefore, the technique is seldom used to study PD plaques.

11.3 Penile MRI

MRI is the main diagnostic imaging approach used to evaluate penile trauma and fracture, penile carcinoma and selected PD patients.

In the latter subjects, MRI has proved less sensitive than US in depicting plaque extension and their relationship with adjacent structures, especially in the case of stable calcified plaques. Gadolinium-enhanced MRI has proved effective in detecting enhancement around plaques as a sign of active inflammation [19] and is more sensitive than greyscale US scanning in assessing non-calcified plaques at the base of the penis [20]. It may also offer valuable information as an objective measure of response to therapy in patients receiving conservative drug treatment.

MRI is considered as a second-line diagnostic approach, but not due to poor diagnostic accuracy or sensitivity, but rather because it cannot be used in routine clinical practice, also due to its poor cost-benefit ratio compared with US, which has become the mainstay of urological and andrological clinical practice.

MRI enables optimal visualization of penile anatomy, but does not provide significant advantages over standard diagnostic imaging techniques.

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Therapy: A General Approach

12

Giorgio Cavallini

Among the most popular treatments in each modality, the urologists' perceptions regarding the suitability of treatment and patient satisfaction were significantly different, indicating the need for development of guidelines based on solid clinical data. Actually Peyronie's disease (PD) guidelines are debatable, as well as any data about this disease [2]. This means that the only statement capable to pacify PD researchers is that PD is characterized by an unpredictable evolution. Thus, no medical or surgical treatment could be planned in the absence of reliable data about the PD evolutive stage: progressive, regressive, or stable disease. Thus, it is difficult to legitimate any treatment (a) in the course of a regressive phase, (b) which cannot stop or revert PD progression.

PD is a disease involving the entire tunica albuginea and is not limited to the plaque [3]; thus, an ideal treatment could not involve the plaque only, with the exception of stable disease.

"Primum non nocere" is a Latin phrase that means "first, do no harm." It derives directly from the Hippocratic oath which states: "I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone." The Hippocratic oath is one of the oldest binding documents in history; the oath written by Hippocrates is still held sacred by physicians. This means that medical treatment should be considered before surgery (as a general rule), because surgery may worsen sexual function while medical treatment does not [1].

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Medical Therapy

13

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13.1 Medical Therapy: A Point of View

A review of published literature on oral, intralesional, external energy, and iontophoresis therapies for PD was performed. Although there are many published reports that show the efficacy of nonsurgical therapies for PD, there is a lack of large-scale, multicenter controlled clinical trials, which makes treatment recommendations difficult. Careful review of the literature does suggest that there are treatment options that make scientific sense and appear to stabilize the disease process, reduce deformity, and improve function. Offering no treatment at all on the one hand will discourage any research in the field and on the other hand will encourage our patients to pursue alternative treatments, which might do harm and misses the opportunity to do some good. Clearly further work is necessary to develop safe and effective nonsurgical treatments for PD.

13.2 A Key for Interpretation of the Efficacy of the Remedies for PD

The difficult nosological classification of PD (see Chap. 5 of the Peyronie disease) has compelled researchers to look for a number of empirical remedies. Some of these remedies could be classified as "historical" like vitamin E, alpha tocopherol [68], procarbazine [15], dimethyl sulfoxide [67], orgotein [58], and hyaluronidase [10] and thus are not discussed, because drugs become unavailable, or any interest was lost because of poor efficacy.

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At present it is difficult to recommend a drug instead of another because double-blind placebo-controlled trials are difficult to perform and data are frequently conflicting. Regardless an analysis of the data of literature demonstrated episodic improvement in the symptoms which could hardly be explained by a spontaneous regression of the disease, further the response to therapy of PD is at least inconstant. If these episodes are of scientific value, they might demonstrate the polymorphic nature of PD which is consistent with the putative nature of replicative disease (see Chap. 5).

13.3 The Role of Reversible Risk Factors

PD is a much more frequent condition in the general population than previously reported. Cigarette smoking may be considered a risk factor for developing PD. If further and more targeted studies confirm that giving up smoking may reduce the risk of developing PD, then there will be new prospects for primary and secondary prevention and for curbing the progression of the disease [40].

Plaque area and pain diminished in patients with diabetes, coincidentally with diabetes compensation and antidiabetic therapy administration. On the other hand, the nondiabetic patients had their plaque area significantly increased, while their pain was not modified. The Spearman tests found a significant correlation between glycemia before diabetic compensation and the percentage of decrease in the size of plaque of patients with diabetes [14].

The plaque area was significantly higher in PD patients with low testosterone than in patients with normal testosterone. Plaque area and penile curvature improved to a greater extent when intraplaque verapamil injections were associated with testosterone administration in hypogonadal men than when associated with a placebo. Men with PD had lower testosterone than healthy controls. In these patients, supplementation with testosterone improved the efficacy of intraplaque verapamil. Plaque area and penile curvature were more severe in hypogonadal PD [12].

Diabetes compensation and/or antidiabetic therapy, stopping the smoking habit, and testosterone replacement in hypogonadic PD patients improved PD symptoms and/or the efficacy of medical therapy.

Almost all studies looking for a medical therapy for PD do not consider reversible risk factors; thus, the differences found in the results of the different studies might reflect differences in studied populations in terms of the presence or absence of reversible risk factors.

13.4 Plaque Therapy: The Myth of a Holistic Approach to PD Therapy

It is felt that intraplaque therapy could not be sufficient for PD because PD is a disease involving the whole tunica albuginea.

In fact both tunica albuginea and PD cultures contain cells, presumably stem cells, that undergo osteogenic and myofibroblast differentiation and may induce

these processes by paracrine interactions. This may explain progression of fibrosis in the PD plaque and its eventual calcification [79].

Further cultured and transplanted cells from PD plaques display a behavior similar to tumor cells; in fact a successful establishment of immortalized cell lines from plaques and normal tunica albuginea from men with PD has been obtained [50, 51].

Alterations of extrinsic and intrinsic apoptotic pathways have been found in plaque and in tunica albuginea of PD patients [45].

Finally, most of the PD plaques remain at a subclinical status; thus, it is not surprising that a new plaque arises in the course of localized therapy of a single plaque [72].

Thus, the general administration of drugs potentially able to inhibit and/or to revert plaque dimensional increase is welcome, at least under a theoretical point of view.

13.5 End Points of Therapy

PD is a progressive disease in the majority of the cases (see Chap. 6); thus, the end point of therapy is stopping the plaque progression [6, 81]. But it is felt that nobody could be angry in the case of plaque reduction.

The authors sustain that the evolution of PD in the course of therapy should be evaluated on the basis of plaque volume, while penile deformity should be evaluated as a last resort. In fact plaque deformity could be improved even by a new plaque on the opposite side of the first; further, the reduction of a single large plaque into two or more smaller plaques might lead a straight but crumpled penis to a curve but uncrumpled penis.

Despite some recent reports about the intraplaque use of collagenase in which the evaluation of the efficacy of the therapy was left to patients' subjective judgment [27], the author believes that an objective instrumental evaluation is more reliable, because patients tend to overestimate penile deformity in the course of PD (see Chap. 9).

13.6 Drugs

13.6.1 Oral Drugs

13.6.1.1 Potassium Para-aminobenzoate (POTABA)

POTABA has been utilized in a variety of disorders characterized by increased fibroblast proliferation and collagen and glycosaminoglycans synthesis including morphea, lichen sclerosus, lichen atrophicus, and rheumatoid arthritis. POTABA has been shown to affect cell replication and macromolecule synthesis of fibroblasts [32, 56].

POTABA showed a statistically significant decrease in plaque size versus a placebo over 12 months and seemed to confer a protective effect against the worsening of penile curvature. However, there was no statistically significant improvement in

erectile curvature from baseline [81]. However, side effects (mainly gastrointestinal) and high cost make difficult to use this drug.

13.6.1.2 Vitamin E (Tocopherol)

Vitamin E was first used in the treatment of PD in 1949. Its property of scavenging free radicals is thought to contribute to improve PD fibrosis [76]. Vitamin E is inexpensive and safe; however, its efficacy does not appear superior to placebo [33, 66]. Nonetheless, it has often been used in combination with other oral, intralesional, and iontophoresis treatments, and interestingly, it does seem to show some synergistic effect [55, 57].

13.6.1.3 Tamoxifen

Tamoxifen's proposed mechanism of action is to decrease fibroblast secretion of transforming growth factor-beta (TGF-β), thereby decreasing fibrogenesis [59]. Tamoxifen has failed to show any statistically significant benefit versus placebo in a prospective controlled trial containing statistical mistakes [77]. Tamoxifen showed a lower efficacy and more side effects than carnitine [9].

13.6.1.4 Colchicine

Colchicine is an alkaloid derived from the autumn crocus, *Colchicum autumnale*. Oral colchicine (1 × 2 mg/day) proved effective in at least three single arm uncontrolled studies [1, 2, 39]. On the other hand, colchicine has proved to be no better than placebo in improving pain, penile deformity, or plaque size in advanced PD [63]. The use of vitamin E associated to colchicine in the early stages of the disease (time from clinical onset <3 months) is a well-tolerated way to improve PD symptoms [57].

Colchicine has been demonstrated to inhibit the in vitro proliferation of fibroblasts from PD plaques and from healthy tunica albuginea [3]. El Sakka et al. evaluated the effects of colchicine in an animal model: colchicine-treated animals exhibited less collagen deposition in the tunica albuginea [24].

The main cellular changes detected were the collapse of the rough reticulum, reduction of myofilaments, and the disappearance of the intracellular widely spaced collagen [22]. The primary action of colchicine is to bind tubulin, thus inhibiting the formation and the function of the spindle during mitosis and the transport of intracellular vesicles [52]. By this way the anti-inflammatory properties of colchicine have been explained. Colchicine may also inhibit the secretion of proinflammatory cytokines and block the formation of eicosanoid by inhibiting phospholipase A2 in monocytes and neutrophils [39].

13.6.1.5 Pentoxifylline

Pentoxifylline (PTX) is a nonselective phosphodiesterase inhibitor with anti-inflammatory and anti-fibrogenic properties. With regard to PD, it acts to prevent TGF-β-mediated inflammation and plaque deposition of type 1 collagen [65]. In its first randomized controlled trial, it was shown to improve the penile curvature, plaque area, and International Index of Erectile Function (IIEF) score versus a placebo [65].

A subsequent retrospective cohort study found significant improvement in penile calcifications over 1 year of treatment when compared to a placebo [73].

13.6.1.6 Phosphodiesterase Type 5 Inhibitors

Despite an excessive industrial pressure to sustain that PDE5 inhibitor tadalafil 5 mg once a day might improve PD symptoms, there are only few reports in this regard.

A steady overexpression of inducible nitric oxide synthase, leading to increased nitric oxide and cyclic guanosine monophosphate (cGMP) levels, seems to act as an endogenous antifibrotic mechanism. This process has also been reported in corporal and cardiovascular fibrosis and has led to the demonstration that long-term continuous administration of phosphodiesterase type 5 inhibitors counteracts the development of a PD-like fibrotic plaque in a rat model and later extended to the prevention of corporal fibrosis in animal models of erectile dysfunction [30]. But these data are far from sustaining the hypothesis of a beneficial effect of tadalafil on PD symptoms.

Tadalafil therapy 5 mg once a day in combination with extracorporeal shock wave therapy (ESWT) was superior to ESWT alone in both IIEF and quality of life scores [53], but these results are not conclusive for the main PD symptoms: pain, plaques, and deformity.

13.6.1.7 Coenzyme Q10

Coenzyme Q10 is a fat-soluble quinone that is a powerful, endogenously secreted antioxidant. Not only does it display antioxidant and anti-inflammatory properties itself, but it is also thought to regenerate other antioxidants within the body. It is a relatively new therapy in the treatment of PD, but in its first RCT, it showed statistically significant improvement in the IIEF score, mean plaque area, and penile curvature when compared to a placebo over the course of 6 months [64].

13.6.1.8 Carnitines

Their role in the treatment of PD stems from their antioxidant properties, via an increase of mitochondrial respiration which in turn increases acetyl-coenzyme A concentration through the availability of acyl groups [18]. Carnitine administration has been shown to enhance cellular immune response by (a) boosting CD4 + T lymphocyte response, (b) inducing a strong reduction in the percentage of both CD4 and CD8 cells undergoing apoptosis, and (c) producing a substantial increase in the rate and absolute counts of CD4 lymphocytes and, to a lesser degree, of CD8 lymphocytes [20].

In a prospective research with 96 patients in 2001, acetyl-L-carnitine showed statistically significant improvement in penile curvature versus tamoxifen [9]. In 2002, propionyl-carnitine demonstrated efficacy in treating advanced and resistant PD when used in combination with intraplaque verapamil, which was superior to tamoxifen plus verapamil therapy [11]. In the most recent prospective research in 2007, however, it showed no superiority to a placebo, either alone or in combination with concurrent vitamin E therapy [66]. In this last research carnitine dosage was much lower (about one-third) than in previous; thus, data are not comparable.

13.6.2 Intraplaque Therapy

The Internet era allows, unfortunately, a number of opinions about the most suitable technique to perform injective therapy for PD: intraplaque, periplaque, and intracavernous administration routes have been made known by several medical doctors.

At present literature legitimate to use intraplaque therapy only.

13.6.2.1 Corticosteroids

First used for the treatment of PD in the 1950s, initial results with ILI of steroids were promising. Subsequent trials, however, failed to reproduce these positive findings, and unfavorable side effects (including local tissue atrophy and fibrosis) made any subsequent surgical interventions more difficult [34].

13.6.2.2 Verapamil

Intralesional injections of verapamil (a calcium-channel blocker) were first used in the therapy of keloids [71], and only later were they used in PD. An intraplaque injection of 10 mg of verapamil was successfully introduced by Levine [42, 43] in single arm uncontrolled studies. He demonstrated that verapamil injection reduced plaque size, penile curvature and pain, and improved sexual potency with few side effects. A randomized blind placebo-controlled study confirmed these data [60]. The dilution of 10 mg of verapamil up to 20 ml for intraplaque injection significantly improves the efficacy of the drug for PD symptoms. It has been postulated that hydrodistention may improve verapamil efficacy by boosting immune reactivity toward plaque components [13]. The efficacy of verapamil for PD symptoms has been further confirmed by Mulhall's group [6].

Penile curvature, immunohistology, and erectile function outcomes have been evaluated after intralesional injections of verapamil and normal saline in a Peyronie disease animal model. This study offers histological evidence of cellular changes and improvement in penile pressure and curvature in rats with the Peyronie plaque after intralesional verapamil injection [17].

Although in these studies verapamil has been found to be effective in the treatment of the Peyronie disease, Shirazi et al. [70] did not find any improvement in comparison with the control group treated with saline.

Nicardipine, a calcioantagonist similar to verapamil, proved to be effective in reducing PD symptoms in a prospective single-blind therapy [74].

Verapamil inhibits the secretion and synthesis of extracellular matrix, including collagen, glycosaminoglycans, and fibronectins, as well as causes increased collagenase and anti-transforming growth factor-beta activity. Verapamil stimulates the degradation and the remodeling of extracellular matrix in tissues by altering the metabolic pathways of fibroblasts [60, 71].

The efficacy of chemotherapy is often decreased by the development of cancer cells resistant to cytostatic drugs. This phenomenon is caused by the activity of the various transporters, i.e., multidrug-resistance (MDR) gene-encoded P-glycoproteins, which pump anticancer drugs out of the cells [8]. Furthermore, there is mounting evidence that P-glycoprotein plays a significant role in the

regulation of apoptosis induced by various stimuli whose overexpression provoked prolonged life spans of monoclonal lymphocytes in B-cell lymphocytic leukemia providing them with a resistance in programmed cell death. Verapamil inhibits the overexpression of P-glycoprotein and of MDR [37]. Verapamil displays direct antiproliferative activity via a nonionic target membrane [62] and/or via a nonselective block K+ channel of the outer cell membrane [83]. As a conclusion verapamil displays regulatory functions on the tumor cell life cycle.

13.6.2.3 Interferon

Duncan first demonstrated the potential use of intralesional interferon-alpha-2-b (IFN-a2-b) in PD patients [23]. Interferons are a group of naturally occurring glycoproteins which play an integral role in the immune system by interfering with viruses and causing antiproliferative and antitumorigenic effects. IFN-a2-b decreases keloids [7]. Most researches indicate an improvement of plaque size, pain, erection, and vascular patterns after intraplaque injection of IFN-a2-b either in uncontrolled or in placebo-controlled trials [35]. These data have been recently confirmed [78]. On the other hand some authors have denied any efficacy of IFN-a2-b in PD symptoms [36, 80].

The author thinks that this variable efficacy of interferon might be caused by a different route of administration (intraplaque or subcutaneous around the plaque), dosage, regimen of administration, and patient selection.

IFN-a2-b proved active as an antiproliferative drug for tumor cells [5, 75] and for fibroblasts [82], inhibiting necrosis, inflammation [26], and oxidative stress [69]; it recognizes previously activated tumor reactive T cells with potent killing ability [4], and it promotes more balanced cytokine responses [19].

13.6.2.4 Collagenase

Collagenase is an enzyme that degrades collagen; thus, it constitutes a logical choice for PD. First used in 1980 for PD [28], collagenase has not yet gained widespread acceptance until recent years. It has also been successfully used in the treatment of Dupuytren contractures, with which PD shares a similar pathophysiology [48].

Interest in collagenase was revived in 2008 when Jordan [38] published a study demonstrating its safety and efficacy in reducing curvature in a small population of patients. In 2013, a large multicenter phase IIb randomized controlled trial showed statistically significant improvement in penile curvature and the symptom bother domain as compared to placebo [28]. Serious adverse effects occurred in approximately 1 % of patients in the collagenase group, the most serious being corporeal rupture requiring surgical repair. Less serious side effects such as swelling, ecchymosis, and pain in the injection site were more common and resolved with conservative treatment.

13.6.3 Topical Treatments

There are few studies about topical therapy of PD including men pretreated with topical verapamil who then immediately underwent surgical correction for their PD. The excised tunica albuginea tissue samples from these PD patients were

examined for the presence of verapamil, which was not seen [46]. These data legitimate a number of doubts about a randomized controlled trial which wanted to demonstrate an improvement in curvature and plaque size in patients receiving topical applications of verapamil (15 % twice daily) over the course of 3 months when compared to placebo [25].

13.6.4 Transdermal Electromotive Drug Administration

Transdermal electromotive drug administration (iontophoresis) provides a higher tissue penetration for the transdermal application of medications.

Dexamethasone + lidocaine + verapamil [61] and orgotein + dexamethasone + lidocaine [49] when administered with iontophoretic equipment improved plaque size, penile deformity, and pain. In fact surgical specimens of tunica albuginea from men pretreated with iontophoresis demonstrated a detectable level of the drug in the majority of patients [41]. Verapamil + dexamethasone proved more active than placebo in reducing PD symptoms [21]. A further research sustained that verapamil alone had no superiority to a placebo (saline) [31]. Curiously an unblinded randomized controlled trial suggested that verapamil administered with iontophoresis had better results than verapamil administered intralesionally [47].

13.6.4.1 Extracorporeal Shock Wave Therapy

The efficacy of extracorporeal shock wave therapy (ESWT) on PD symptoms is questionable. Palmieri showed that ESWT + tadalafil induced significant improvements in the IIEF score and quality of life in patients; this effect was superior to the sham treatment; however, there was no statistically significant improvement in penile curvature or plaque size from baseline [55]. A small randomized controlled trial by Chitale et al. [16] in 2010 showed no difference between patients receiving ESWT and sham therapy in any primary outcome measures (plaque size, curvature, IIEF).

13.6.5 Penile Traction Therapy

Two small trials published in 2008 by Levine et al. [44] and in 2009 by Gontero et al. [29], respectively, showed only mild success with daily use of PTT over the course of 6 months. In the second trial, these results were not statistically significant and found to be largely unsatisfactory to the patients involved.

Conclusions

Challenges in the treatment of PD are multifactorial and grounded on empirical, but biologically correct, principles. Each challenge displays success and failure; this disagreement is hardly explained with poor experimental design and/or poor patient selection and/or other reasons different from PD polymorphic nature. These considerations legitimate the next chapter about multifactorial therapy.

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Combination Therapy (in the Treatment of Peyronie's Disease)

14

Gianni Paulis

14.1 Combination Therapy or Multimodal Therapy

14.1.1 Definition

Multimodal therapy (MMT) is a term coined by Arnold Lazarus and derived from psychotherapy. MMT means that there are multiple modalities of each patient that should be addressed when both identifying and treating a psychological disorder.

According to this concept, each patient should be treated accordingly in order for treatment to be successful [1].

In our different field of action, we believe that the concept may be applied in order to achieve a better therapeutic outcome. In the medical field and in our subject (Peyronie's disease), the object is no longer the individual, but the particular individual's disease.

Therefore, with a similar argument we can devise a treatment plan that includes several therapeutic substances and/or treatment modalities in order to achieve greater results than each single drug or treatment modality.

Similarly, tuberculosis was treated with combination therapy over the last 60 years and more, because therapeutic regimens that use only a single drug result in the rapid development of resistance and treatment failure [2–5].

Analogously, in the field of oncology, malignant tumours were treated with combination therapy over the last 60 years. The possibility that more effective cancer chemotherapy may be achieved by treatment with combinations of two or more agents has received attention the first time in 1952 (Shapiro) [6];

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however, studies on the same subject had already been published in 1941 and 1949 [7, 8]. At the present time, this therapeutic proposal retains its validity and effectiveness [9].

In the field of urology/andrology, and specifically in Peyronie's disease (PD), in the last century there have been many studies that have experienced something of a "combination therapy".

However, they were simple therapeutic proposals to improve the chances to cure Peyronie's disease better [10–14]. For the first time, Pastorini et al. experienced the association between local injection and oral therapy [14]. These authors reported their experience of the PD treatment using injection and per os superoxide dismutase therapy associated with vasoactive FIC. Their study showed that pain disappeared and penile incurvation improved in the majority of patients.

In recent years, in uro-andrologic literature, the studies that have suggested a "combination therapy" were more interesting and better structured, but especially in some of these investigations, the concept of multimodal therapy is clarified and pointed in order to achieve best results.

14.2 Main Studies Related to Combination Therapy in Peyronie's Disease

14.2.1 Lamprakopoulos et al. (2000)

In this study the authors experimented in patients with Peyronie's disease a combination of more substances in the same penile injection [15].

The authors assessed the association of betamethasone, hyaluronidase and lidocaine.

One hundred twelve men patients with a palpable penile plaque suffering from painful erection and bending of penis were treated with 12 penile injections containing betamethasone, hyaluronidase and lidocaine. Patients were classified into groups according to the size of the plaque (<10 mm, 10–20 mm or >20 mm) as well as the disease duration (<6 months, 6–12 months or >12 months).

Evaluation of patients and assessment of outcome were based on subjective criteria, while measurement of plaque size was made by means of ultrasound.

Results were correlated to previously mentioned patients' characteristics. After treatment, painful erection, bending of penis and plaque were absent in 97 %, 32 % and 31 % of patients, respectively, after treatment. The outcomes of this study were characterised by a high response rate in patients with a history of less than 12 months and a penile plaque not exceeding 20 mm in length.

Although the study lacks a control group or placebo group, the outcomes indicate a very good response. Stratification of PD patients according to disease duration and the plaque size has allowed a very interesting analysis of the results.

14.2.2 **Cavallini et al.** (2002)

The authors conducted their research in order to verify the usefulness of the combination oral propionyl-L-carnitine plus intraplaque verapamil for advanced or resistant Peyronie's disease [16].

The combination of the two drugs was evaluated in two studies.

In the first group 60 patients affected by advanced PD were randomised in two subgroups treated with verapamil intraplaque injection (10 mg weekly for 10 weeks) plus oral administration of propionyl-L-carnitine (2 g daily for 3 months) or verapamil intraplaque injection (10 mg weekly for 10 weeks) plus oral administration of tamoxifen (40 mg daily for 3 months).

In the second study, 15 patients with resistant PD (to previous therapy) were treated with verapamil intraplaque injection (10 mg weekly for 10 weeks) plus oral administration of propionyl-L-carnitine (2 g daily for 3 months).

In the first study, pain was reduced in both subgroups.

Propionyl-L-carnitine plus intraplaque verapamil significantly reduced penile curvature, plaque size and disease progression. In addition, this association of drugs significantly improved the erectile function.

Tamoxifen plus intraplaque verapamil had none of the therapeutic effects of the previous association of drugs.

In the second study propionyl-L-carnitine plus intraplaque verapamil has modified positively the disease patterns as in the first.

The authors concluded that the combination of propionyl-L-carnitine and verapamil was effective for the treatment of choice for advanced PD.

The study was very significant because it included a control group and a reliable statistical study (differences between subgroups or the variables compared using analysis of variance). In addition, the research was very important and significant to introduce the concept of "combination therapy" in PD.

14.2.3 **Prieto Castro et al.** (2003)

In their study the authors assessed the effectiveness of the combination of colchicine and vitamin E in the treatment of PD [17].

In these 45 patients, the time from onset of the disease was <6 months; in all cases penile curvature was <30°; none of the patients had erectile problems.

Forty-five patients were divided into two groups and treated as follows:

- First group: 22 patients who received ibuprofen 400 mg daily for 6 months
- Second group: 23 patients who received a combination of vitamin E 600 mg daily plus colchicine 1 mg every 12 h

Penile pain, plaque size and penile curvature were assessed at 6 months.

After treatment, statistical analysis of the results revealed significant differences in plaque size and penile curvature in those patients who received colchicine plus vitamin E.

The authors concluded that the combination of colchicine plus vitamin E during the early stages of PD and with mild penile curvature and without erectile dysfunction is an effective way to stabilise the disease.

Although this study lacked a control group with one of the substances included in combination, it has shown the efficacy of combination therapy (colchicine plus vitamin E) in the treatment of PD.

14.2.4 **Cakan et al.** (2006)

The authors conducted this study to find out if smoking has an effect on the results of therapy with vitamin E plus colchicine in PD patients (early stage) [18].

Fifty-eight patients affected by early-stage PD without calcified plaque and without erectile dysfunction were included in the study. The time from onset of the disease was less than 6 months.

These patients were divided into two groups: smokers (group 1, 36 patients) and non-smokers (group 2, 22 patients). All patients were treated with vitamin E (800 IU daily) plus colchicine (1 mg daily) for 6 months.

It is interesting to note in the results that decrease in penile curvature and plaque size was significantly higher in group 2 (PD patients, non-smokers).

The study is interesting because in addition to confirming the validity of the "combination therapy" in treating PD, it reveals one of the risk factors associated with the progression of this disease [19] (see Sect. 13.3).

14.2.5 **Candebat Montero et al.** (2008)

It is a study in which 96 patients affected by Peyronie's disease were treated with interferon, laser and their association [20]. Authors divided all patients into three treatment groups: interferon, laser and interferon + laser. Treatment was started and continued for 28 weeks. The dose of recombinant human interferon alfa-2b (IFN-α-2b) injected intraplaque (weekly) was ten million IU.

Final outcomes with combined IFN-α-2b + laser were significantly better than the other treatment groups: improvement of symptoms (pain) 84.7 %, decrease of plaque size 90.6 % and decrease of penile curvature 87.5 %.

The authors concluded that the combination of both therapies (interferon + laser) resulted to be more effective than each of them separately.

This study is very interesting because "combined therapy" which has been proposed consists of two different treatment modalities: pharmacological therapy (local penile injection) + physical therapy (laser therapy).

14.2.6 **Taylor and Levine** (2008)

Although this paper represents a review of the literature concerning the medical therapy of PD, the authors conclude by proposing a multimodal approach for non-surgical therapy of PD [21].

The proposed multimodal approach includes pentoxifylline orally (400 mg three times a day), L-arginine 1,000 mg twice a day, intralesional verapamil injections and the use of penile extender (Extender FS, FS Physiomed).

14.2.7 **Cortés-González and Glina** (2010)

These authors in their retrospective study evaluated 100 patients affected with PD [22]. The patients were divided into two groups: group colchicine as monotherapy (CM) oral colchicine 1.5 mg/day, 59 treated patients, and group colchicine/vitamin E (CVE) orally 1.5/800 mg/day, 41 treated patients.

Good response to treatment was observed in 39 % vs 41 % in the CM and CVE groups, respectively.

Although the outcomes were not statistically significant, the authors concluded supporting the theory of a combined treatment in Peyronie's disease.

14.2.8 **Kuehhas et al.** (2011)

It is an article review concerning new developments for nonsurgical treatment strategies for PD [23]. After a careful and detailed overview of conservative treatment options for PD treatment, the authors emphasised that no single oral medication should be recommended as a treatment option for patients in the acute phase of PD. They then concluded that the best approach is multimodal therapy.

14.2.9 **Larsen and Levine** (2012)

This is a review of the contemporary literature on nonsurgical therapies for Peyronie's disease (PD) and review of the latest guidelines for the management of PD from the international consultation on sexual medicine (ICSM) [24]. After a careful analysis of all the conservative therapeutic methods for PD, the authors concluded that a combination of pharmacological substances (oral agents and/or intralesional injection) with penile traction device may provide a synergy between the chemical effects of the drugs and the mechanical effects of traction.

14.2.10 Abern et al. (2012)

The authors performed this study to evaluate the effectiveness of penile traction therapy (PTT) when associated with intralesional verapamil injections combined with oral L-arginine (1 g two times daily) and pentoxifylline (400 mg three times daily) in PD patients [25]. Seventy-four PD patients were studied and divided into two treatment groups: group I (39 patients), verapamil injections (12 total) + oral therapy (L-arginine + pentoxifylline) + penile traction therapy (for 2–8 h daily and no longer than 2 h per session), and group II (35 patients), only verapamil injections (12 total) + oral therapy (L-arginine + pentoxifylline). The mean improvement of penile curvature was 26.9° in group I vs 20.9 in group II ($p=0.22$). The mean PTT use was 3.3 h/day, and patients with >3 h/day use gained 0.6 cm in penile length vs 0.07 cm using less than or equal to 3 h/day ($p=0.09$). There was a greater improvement in penile curvature and a significant increase in the length of penis in patients who were treated with combination therapy protocol.

As in other researches, this study demonstrated the efficacy of combination therapy in PD treatment.

14.2.11 Halal et al. (2012)

In this study the authors studied 350 patients diagnosed with Peyronie's disease [26]. The patients were divided in three groups of treatment: group I, 125 patients treated with intralesional injections of verapamil; group II, 100 patients treated with vitamin E and colchicine; and group III, 125 patients treated with verapamil, vitamin E and colchicine.

Treatment protocol included 10 mg verapamil, one injection per week for a period of 12–15 weeks, 200 mg vitamin E twice daily in combination with colchicine 1 mg twice a day for a period of 3–6 months and the association of the three therapeutic agents for a period of 3 months.

The best results were achieved in the third group (association between verapamil, vitamin E and colchicines): pain resolved completely or partially in 95 % of the patients; curvature level decreased by 20–45 in 65 % of the patients; plaque size decreased to about 60 % of the patients; erectile dysfunction was improved in about 85 % of the patients.

This study showed that the combination between oral therapy and intralesional agents can improve the quality of life of the patients with Peyronie's disease.

14.2.12 Levine (2013)

This article is a review of the current nonsurgical treatment options for Peyronie's disease [27].

Having analysed the various conservative nonsurgical treatments for the treatment of PD, the author concluded that the combination therapy has the greatest

potential of success for the treatment of PD. The goal is to create a synergy between the chemical effects of the selected oral and injectable drugs combined with the mechanical effects of external traction or vacuum therapy.

14.2.13 Favilla et al. (2014)

The authors evaluated the efficacy of the association of intralesional verapamil injections (ILV) with oral antioxidants (Peironimev-plus® one tablet daily = vitamin E 36 mg, para-aminobenzoic acid 100 mg, propolis 100 mg, blueberry anthocyanins 80 mg, soya isoflavones 50 mg, Muira Puama 25 mg, damiana 25 mg and *Persea americana* 25 mg) for 3 months [28].

One hundred five patients affected were randomised and divided in two groups: group A (n. 52 patients) ILV 10 mg weekly for 12 weeks and group B (n. 53 patients) ILV 10 mg weekly for 12 weeks + antioxidants orally one tablet daily for 3 months.

After treatment no significant differences were observed between both groups in plaque size and penile curvature, while significant differences were found relative to orgasmic function (IIEF-OF), intercourse satisfaction (IIEF-IS), overall satisfaction (IIEF-OS) and pain/visual analogue score (VAS) in group B compared with group A.

Based on the positive results achieved in their study, the authors concluded suggesting that the treatment with oral antioxidant should be considered in combination with intralesional verapamil injections to associate multiple mechanism of action and be more effective for the improvement in sexual function.

Conclusions

In most cases the studies mentioned previously always present a comparison between different groups. Various combinations of therapies were listed and presented as potential treatments for PD.

As several authors have written previously, the goal of combination therapy is to combine different mechanisms of action to enhance improvement in deformity, in erectile function and in pain (when present).

Also we have published several studies which have conclusively demonstrated the efficacy of the combination therapy in the treatment of PD [29–33]. Note that in all the studies, a control group is present. In our opinion, in case of the early phase of PD, the more appropriate therapeutic strategy is certainly a treatment that includes antioxidants associated with other antifibrotic substances.

In case of medical treatment of PD, "monotherapy" should be avoided; instead, the "combination therapies" should be preferred in order to achieve higher success.

At present, the scientific research concerning the therapeutic options for PD suffers from a lack of prospective, randomised, placebo-controlled clinical trials with uniform standardised assessments and objective measures of signs and symptoms of this disease (curvature or simple deformity, pain, erectile function

and plaque size). However, although further studies are needed to confirm our hypothesis, we believe that the series of studies previously reported and discussed are quite sufficient to propose the concept of "combination therapy" in the treatment of Peyronie's disease.

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Surgical Therapy for Peyronie's Disease: Why and When (An Overview)

15

Enrico Spera and Anastasios D. Asimakopoulos

Peyronie's disease is a fibrotic wound-healing disorder of the tunica albuginea [1]. Although it may be precipitated by either blunt penile trauma or trauma incurred during sexual intercourse, as much as 70 % of Peyronie's disease is idiopathic, without an inciting event [2]. Most commonly, the associated penile deformity is characterised by penile curvature, although other features may include palpable penile plaques, hourglass defects, penile hinging/instability and penile shortening [3]. Additionally, there may be associated psychological distress for the patient and the partner, as well as relationship strife [4].

The natural history of PD has two phases. First is the active (or acute) phase, characterised by active inflammation and progressive deformity of the erect penis. Penile pain, when present, also occurs at this time [5]. The acute phase generally lasts from 6 to 18 months, and after this phase, the vast majority of patients go on to have stabilisation of the plaque or progression of their disease [6]. This stabilisation process is characterised by fibrosis, dystrophic calcifications and, rarely, ossification and occurs in the chronic (or latent) phase. After the acute phase has ended, only 10–15 % of patients will have spontaneous resolution of PD, although many will experience resolution of their associated pain [6].

The pathophysiologic basis for PD relates to the inflammation seen in the acute phase and the subsequent disordered wound-healing characteristics of the chronic phase [5].

A multitude of medical and nonsurgical treatments have been attempted for this potentially debilitating disease, without much evidence-based data supporting their use [5]. This multitude of treatment options for PD is a reflection of their relative ineffectiveness, and the lack of a nonsurgical 'gold standard' of treatment has made it difficult to compare the relatively few randomised controlled trials that do exist

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[7–13]. Finally, the natural history of the disease in two distinct pathophysiologic phases (acute and chronic) further muddles the assessment of the treatment response, since treatments appropriate at one time may not be effective at another. This is compounded by a variable disease course that can progress, regress or, rarely, even resolve, without any treatment at all [5].

Nevertheless, it seems that conservative treatments for Peyronie's disease should resolve painful erections in most men [14]. However, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct the curvature and allow satisfactory intercourse [15]. Since it is estimated that up to 20 % of men who have Peyronie's disease will have resolution of the pain and stabilisation of the curvature within the first 12 months of their condition onset, medical experts suggest waiting a full year before attempting to correct it surgically [3]. Consequently, the natural history of the disease (acute versus chronic phase) must be carefully determined in the preoperative setting, as *surgical intervention is not recommended within the first 12 months after the disease onset or before penile deformity has been stable for at least 6 months*.

On the other hand, although some men may improve their curvature spontaneously, many men will progress over the first 12 months and have persistent and complete inability to achieve penetration because of either the magnitude of the penile curvature or secondary erectile dysfunction (ED) [14].

Surgery is indicated when Peyronie's disease is stable for at least 6 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms, and intercourse is compromised due to deformity (level of evidence 3, grade of recommendation C) [14, 16]. The presence of intralesional calcifications could be another indication for the surgical treatment, as these lesions are traditionally less amenable to nonsurgical treatments [5].

The risks of penile shortening, erectile dysfunction, and penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin and the potential need for circumcision at the time of surgery should be adequately discussed with the patient during the informed consent process [16].

Two major types of repair may be considered for both congenital penile curvature and Peyronie's disease: *penile shortening and penile lengthening procedures* [3, 14, 17]. Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. While the penile degloving with associated circumcision (as a means of preventing postoperative phimosis) is considered the standard approach for all types of procedures [17], recent data suggest that circumcision is not always necessary, e.g. in cases where the foreskin is normal preoperatively [18]. Finally, in patients with Peyronie's disease and erectile dysfunction not responding to medical treatments, the surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [19].

Based on the aforementioned data, it is clear that the choice of the most appropriate surgical intervention is based on the (i) preoperative erectile function, (ii) preoperative erectile length, (iii) the magnitude and complexity of the curvature and (iv) patient and partner expectations and goals [14].

Briefly and according to the most recent guidelines of the European Association of Urology [14], *if the degree of curvature is less than 60° and in the absence of any associated deformity (waisting, hinge and hourglass effects), penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. If the degree of curvature is over 60° or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible*. This group of procedures involves the complete or partial excision of the plaque or its incision with the placement of a graft into the space left by the excision/incision technique [3]. Multiple graft materials have been used, including autologous grafts, allografts (same species, e.g. of cadaveric origin), xenografts (unlike species, e.g. of animal origin) or synthetic grafts; however, the ideal grafting material (i.e. inexpensive, readily available, durable, nonreactive/inflammatory, harmless to erectile function and devoid of penile shortening risk) has yet to be identified [3, 14]. Ideal candidates for this approach are men with shorter penile length, irrespective of their degree or complexity of curvature, who have normal erectile function preoperatively. Men who present with hourglass deformity or waisting are also best served by plaque incision and grafting [3, 14]. Grafting procedures are associated with erectile dysfunction rates as high as 25 %. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17 % reoperation rate [20]. *If there is erectile dysfunction, which is not responding to pharmacological treatment (both phosphodiesterase-5 inhibitors and intracavernous penile injections with vasoactive medications), the best option is the implantation of an inflatable penile prosthesis, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis)* [3, 14]. The excellent postoperative patient satisfaction rates are combined with the low incidence of the risks and complications of penile prosthetic surgery (infection, malfunction, reoperation).

In conclusion, while the medical and nonsurgical treatments most likely should resolve the painful erections, the surgical correction of Peyronie's disease with or without penile prosthesis placement remains the gold standard to correct the penile deformity, allowing for a satisfactory intercourse. The presence of active disease (expressed as pain, deformity deterioration or absence of intralesional calcifications on the diagnostic ultrasounds) is an absolute contraindication for the surgical treatment. A detailed and comprehensive consent process should explain to the patient the potential limitations of the surgery in order to set appropriate expectations, thus improving postoperative satisfaction. Issues such as the preoperative erectile function, preoperative erectile length, magnitude and complexity of the curvature and patient and partner expectations should guide the choice among the multitude of penile shortening and penile lengthening procedures.

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Advanced Techniques of Plication Surgery with Basal Approach: When and Why

16

Giovanni Alei and Piero Letizia

Penile curvature consists of an alteration in the shape of the penis when erect which instead of being straight is curvilinear on one or more planes. Penile curvature can be congenital or acquired. The curvature can be ventral, dorsal, lateral or mixed, and it can be associated with urethral malformations. Congenital penile curvature can be caused by an abnormal growth of the corpora cavernosa, the tunica albuginea or both [1].

Acquired penile curvature can be caused by penile fractures or traumas or by Peyronie's disease, also called induratio penis plastica (IPP) (Fig. 16.1).

The disease was observed for the first time in 1743 by the French surgeon Francois de La Peyronie, the physician of King Louis XV, who was affected by penile pain and curvature during erection. He was the first to describe this disorder, which is now referred to as Peyronie's disease. Two phases of the disease can be distinguished. The first is the acute inflammatory phase, which may be associated with pain at rest or during erection. The second is the stabilisation phase, identified by formation of hard palpable plaques that can be fibrotic or calcified and by the presence of penile curvature [2]. The treatment consists of oral drugs and topical treatments such as the association of laser therapy and ionophoresis during the active phase [3].

The surgical approach is restricted to the phase of stabilisation. In this phase the patient can present with penile curvature, erectile dysfunction and penile shortening. These problems can occur singularly or in combination. Surgery is indicated only in patients with stable disease for at least 2 months, without variations in penile curvature [4].

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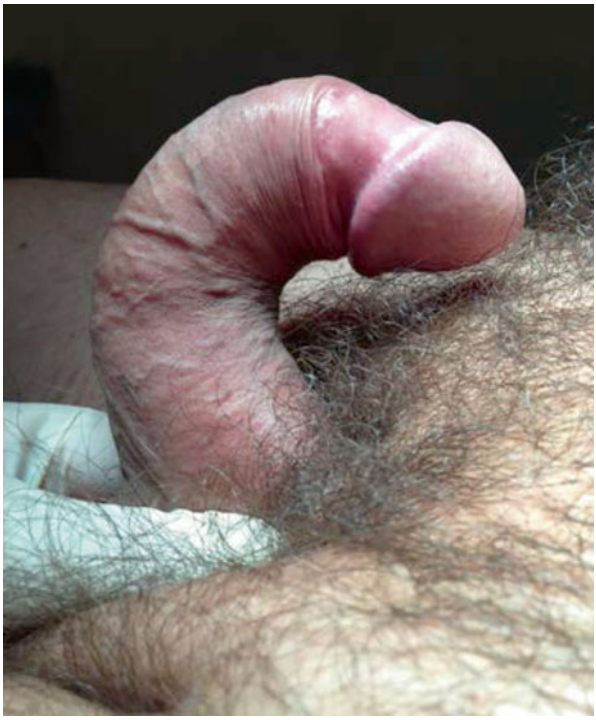

Fig. 16.1 Dorsal penile curvature due to IPP

Possible surgical techniques are:

- Straightening corporoplasties, in case of sufficiently long penis
- Plaque surgery, which lengthens the penis but can cause erectile dysfunction
- Straightening corporoplasty in association with penile lengthening, in order to compensate the shortening due to the corporoplasty
- Penile prosthesis implantation, even in association with fracture of the plaque or plaque surgery in order to lengthen the penis

Corporoplasties can either shorten the longer convex side of the penis (Nesbit operation and its modifications) or lengthen the shorter concave side (plaque surgery) [5]. Several surgical techniques for the correction of penile curvature have been described over the last few years.

16.1 Nesbit and Modified Nesbit Operations (Nesbit II, Kelami)

The first operation to correct penile curvature was described by Nesbit in 1965 [6]. It consists of the removal of tunical ellipses on the convex aspect of the penis at the site of major bending of the corpora cavernosa, so as to shorten the convexity and correct the curvature (Fig. 16.2).

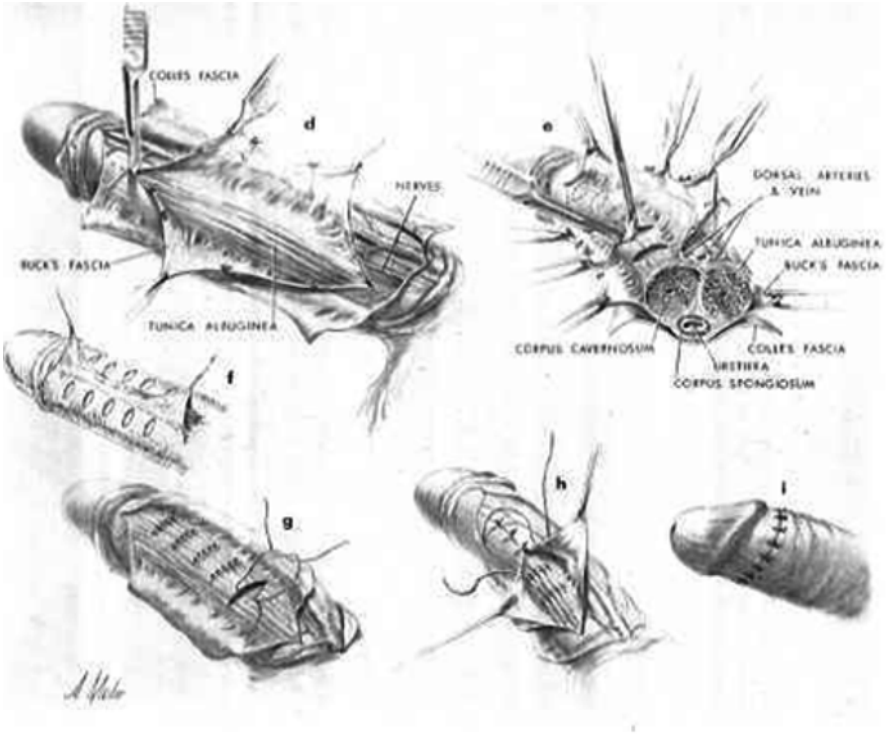

Fig. 16.2 Original drawing of Nesbit technique

This technique involves circumcision and complete degloving of the penis. The number of ellipses to remove, their size and positions are decided intraoperatively, under hydraulically induced erection, by clamping the tunica albuginea with an Allis clamp in order to simulate the correction (Fig. 16.3).

However, the above-described procedure presents a 25–30 % recurrence rate due to a loss of tension of the suture. Moreover, it causes a considerable penile shortening, especially in patients with dorsal or ventral bending. Other reported complications are unsightly suture tracks, circumcision outcomes, postoperative haematoma, skin adhesions and loss of sensation in the glans due to neurovascular impairment.

The Nesbit technique is extremely simple and easy to perform; as such it is still commonly performed. Various modifications to Nesbit procedure were proposed after its introduction, all of which require circumcision to expose the corpora.

The high occurrence of complications, such as erectile dysfunction (20–32 %), recurrence of curvature (15–33 %), altered sensation (4–10 %), painful and palpable nodules (16–66 %) and blemishes following circumcision, leads to the development of alternative techniques [7–12].

In the early 1990s, we described a new technique with a different surgical access (basic penile access vs distal access) and a different type of corporoplasty (double-breasted corporoplasty) [13].

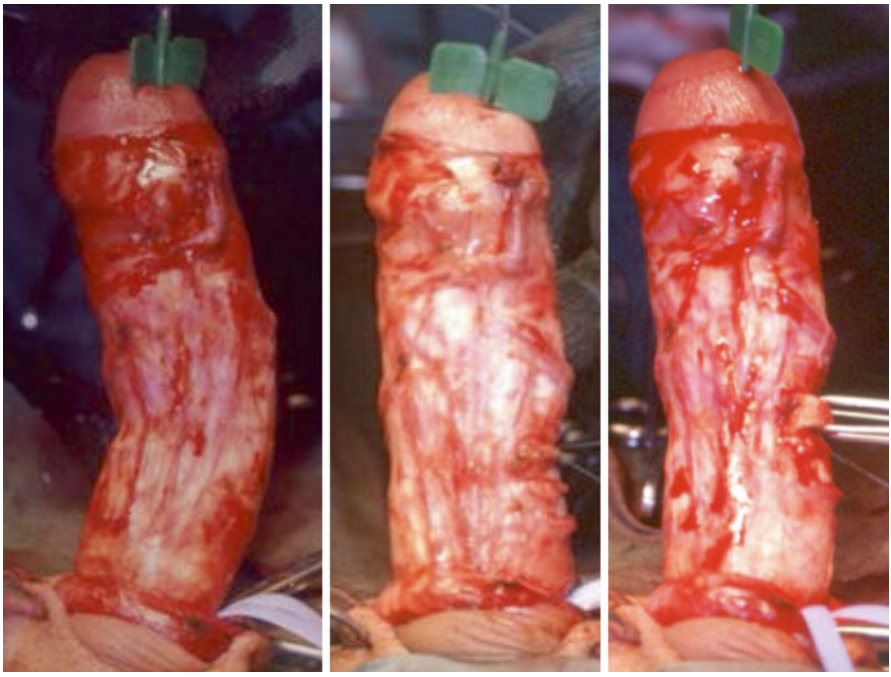

Fig. 16.3 Nesbit II technique

16.2 Alei I Technique

Our technique does not involve circumcision or subcoronal incision [14]. This technique consists of a dorsal basic penile access for ventral bending (Fig. 16.4) or a scrotal access for dorsal and lateral bending, with no consequences on penile sheaths nor alterations in sensitivity [15].

When using this technique, it is very important to perform accurate preoperative measurements of the position and dimension of corporoplasty because the operation is performed during flaccidity and hydraulic erection is only used intraoperatively to confirm the correction (Fig. 16.5).

The advantages of this procedure consist of avoiding circumcision and degloving and operating with flaccid penis on the points identified preoperatively during drug-induced erection [16]. The asymmetry of the suture, with more overlapping of the flaps on the midline and less laterally, allows the correction of penile curvature with a minimal shortening, both in dorsal and ventral curvatures. A scrotal incision of a 3 cm is made (Fig. 16.6) and degloving of the penis, and after placing a tourniquet at the root of the penis, Buck's fascia is prepared at the point where the corporoplasty will be carried out (Fig. 16.7).

The tunica albuginea is opened transversely on the predetermined points and separated from the underlying cavernosus tissue in order to obtain two flaps, a distal

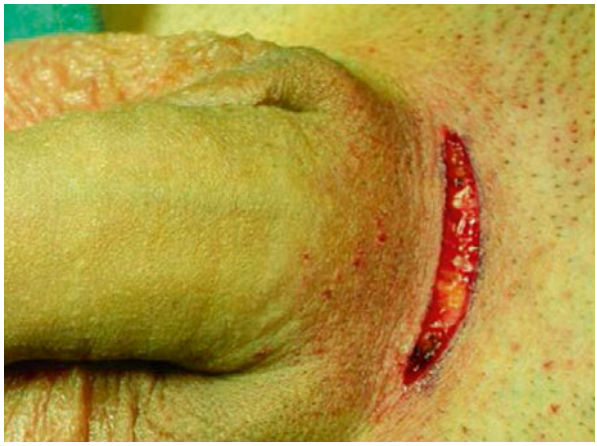

Fig. 16.4 Transverse dorsal basic penile incision

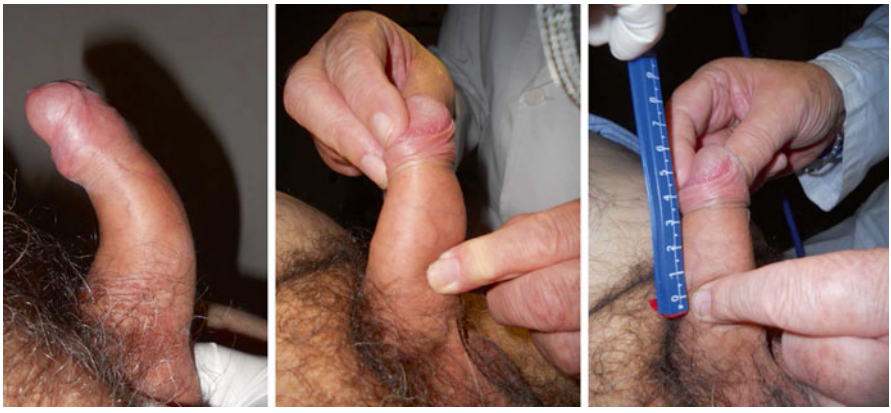

Fig. 16.5 Assessment of the points of correction

and a proximal one (Fig. 16.8), that are overlaid and sutured with a double-breasted corporoplasty using interrupted 2-0 polyglactin (Vicryl®) stitches (Fig. 16.9).

It is important that these sutures are placed asymmetrically in order to overlap more tissue on the point of maximum curvature (Fig. 16.10).

Then, the obtained correction is evaluated by inducing a hydraulic erection. The corporoplasty is completed using a 2-0 running polyglactin suture on the free edge of the albuginea to ensure against leakage. A 2-0 nonabsorbable synthetic multifilament suture is placed crosswise at the point of maximal traction in order to avoid possible recurrence due to early resorption of underlying sutures. Compared to other techniques a lower recurrence rate (4 %) is reported; this is because the overlapping of the tunical flaps provides solidity and physical resistance to distension during the erectile phase. Moreover, a significantly less evident shortening of the penis is observed compared to Montague corporoplasty due to the asymmetrical

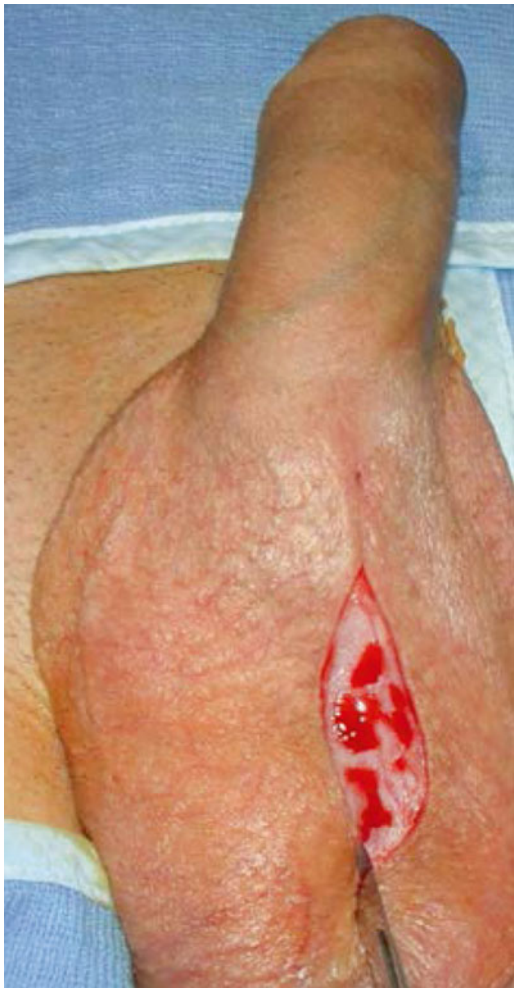

Fig. 16.6 Scrotal incision

suture of the albuginea, as well as the absence of paresthesias or iatrogenic anaesthesias due to the degloving without scalping (Fig. 16.11).

For the penile ventral curvature repair, an infrapubic transverse dorsal incision is made to correct a ventral curvature or when removing or cutting the plaque in Peyronie's disease. Colles' fascia is opened with forceps, and Colles' space is expanded to separate the tissue planes (Fig. 16.12), a technique we have described for phalloplasty for penis enlargement [17]. The Babcock clamp holds the fascia at the point where we will carry out the corporoplasty. The corpora cavernosa are clamped with an Allis clamp opposite the Babcock clamp at the level of the space between the corpus spongiosus and the corpus cavernosus. Buck's fascia is then prepared starting from this point, being careful not to damage the nerve fascia. The dorsal neurovascular fascia is then expanded to expose the dorsal portion of the intercavernous septum. In this way, the tunica albuginea is completely isolated from Buck's fascia. At this point, 'double-breasted' corporoplasty is carried out (a double-breasted procedure is widely used in the surgical repair of hernias).

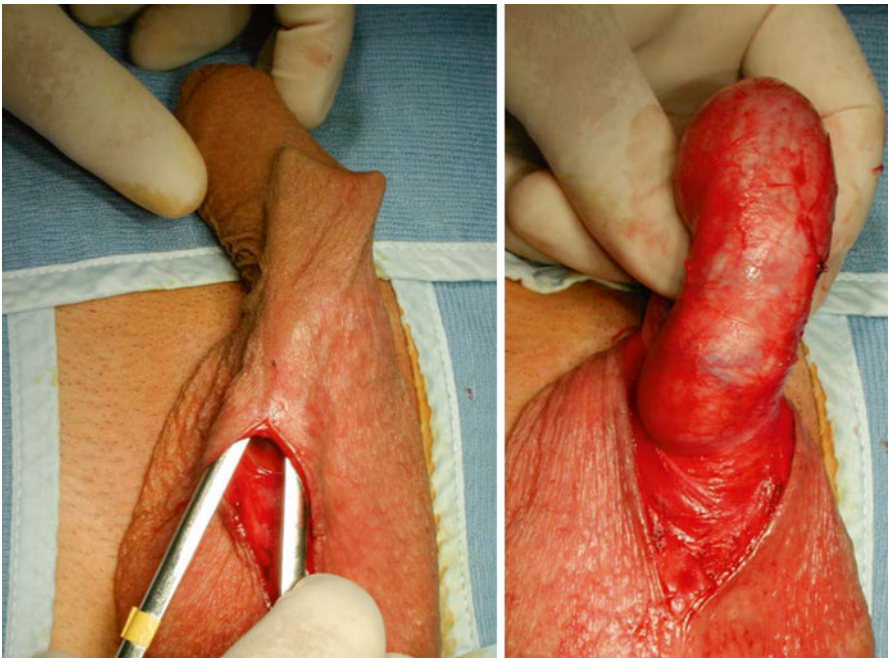

Fig. 16.7 The penis is degloved through the scrotal access

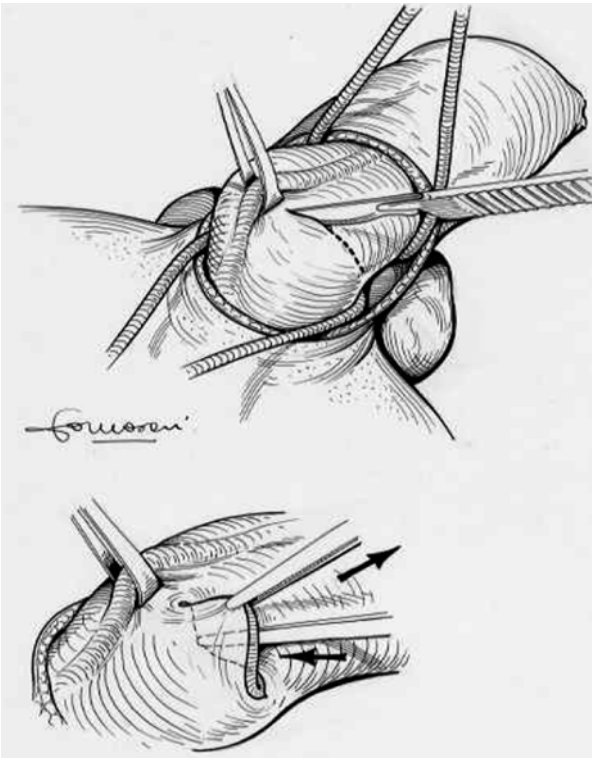

Fig. 16.8 Schematic drawing of the dorsal incision of the tunica albuginea

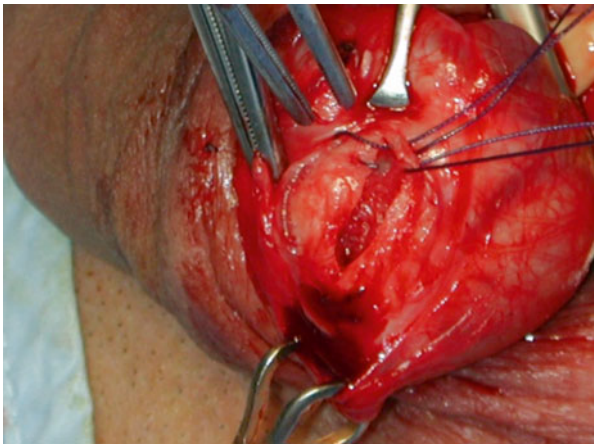

Fig. 16.9 Double-breasted suture

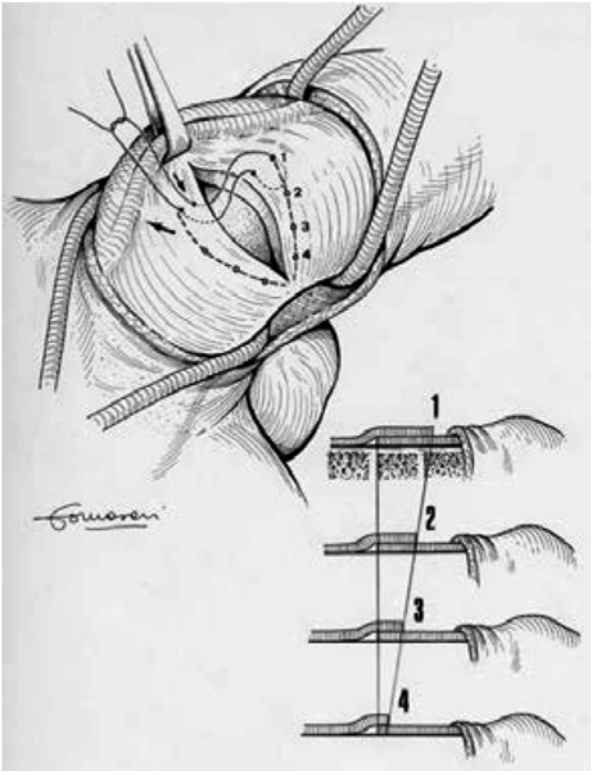

Fig. 16.10 Schematic drawing of the double-breasted suture

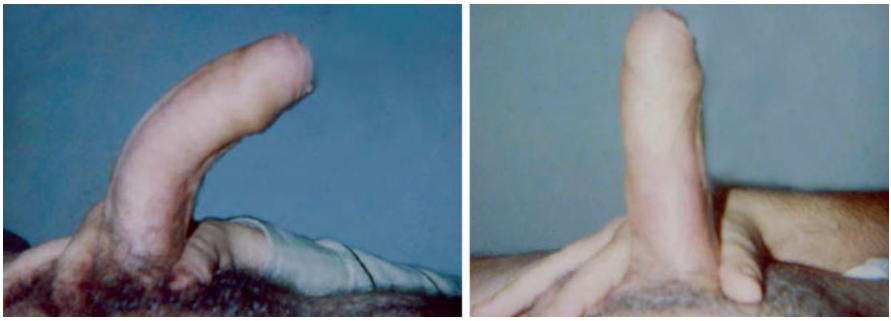

Fig. 16.11 Pre- and postoperative images

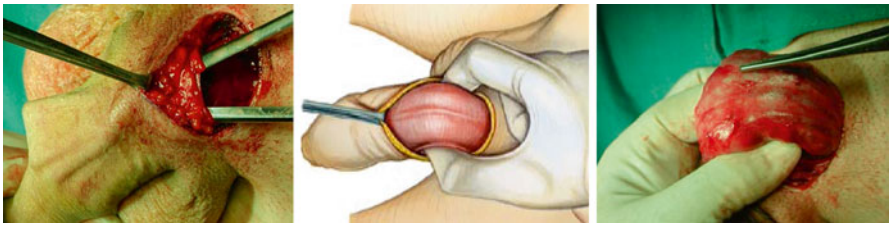

Fig. 16.12 The penis is degloved through the dorsal infrapubic access

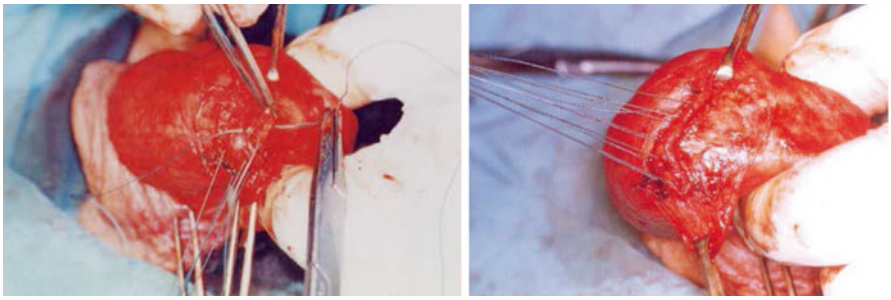

Fig. 16.13 Placement of double-breasted sutures

Five interrupted 2-0 polyglactin (Vicryl®) sutures are placed asymmetrically in a 'U' shape. The amount of the albuginea tissue for overlaying is obtained from the difference between the length of the concave and the convex sides [18] (Fig. 16.13).

The healing time and the number of dressing changes are considerably reduced due to the basic penile access and the absence of oedema and postoperative pain. The Alei technique offers undeniable advantages; however, it has a longer operative time (Fig. 16.14).

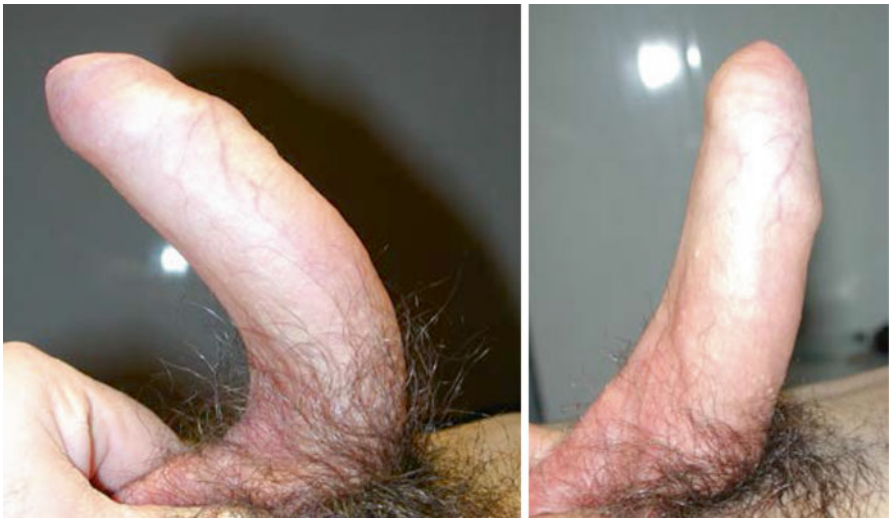

Fig. 16.14 Pre- and postoperative images

16.3 Alei II Technique

The demand for shorter operative time and hospital stay leads us to develop a minimally invasive technique that could reduce the costs and require a short learning curve. In 2012, we developed a new surgical technique for the correction of congenital and acquired penile curvature called 'track' corporoplasty or Alei II. The preoperative assessment includes physical examination and measurement of penile curvature after PGE1 injection with photographs of the orthogonal, frontal and sagittal planes. The next step is to decide where the corrections on the convex side need to be made. Leveraging on the glans by placing the other hand in opposition at the point of greatest curvature, we decide if we need to make one or more corrections, which will depend upon the radius of the curvature in question. The penis is straightened using a finger as a lever at the ideal point of correction. The distance between this point and the external urethral meatus is then measured. The distance between the meatus and the fulcrum at the point of maximum curvature is measured, and photographs are taken in order to guide the surgeon during the operation, as it is performed in a flaccid state, and to show the patient the postoperative result in terms of shape and size of the penis (Fig. 16.15).

The patient is shown the photographs, so that he will appreciate the change that will occur in his penis, and the postoperative photographs must be comparable to the preoperative photographs. This has great significance from the medicolegal point of view because the patient will not be able to say later that his penis is shortened because he was shown that the shortening concerns the convexity that will have to be corrected to the same length as the concavity. Having these measurements is essential because, differently from the Nesbit procedure, we do not

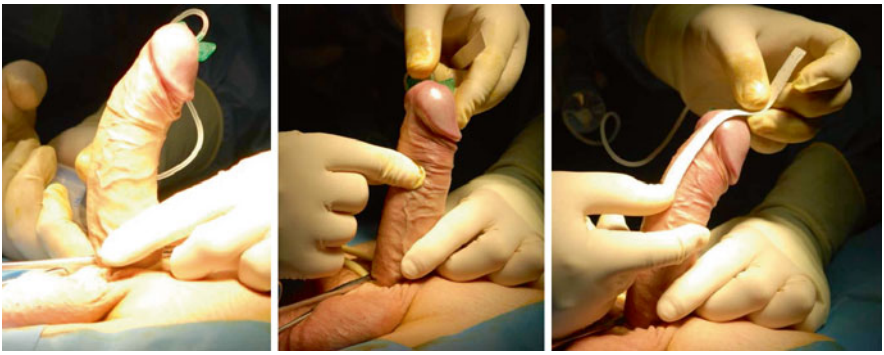

Fig. 16.15 Intraoperative evaluation of the points where to perform the 'track' corporoplasty

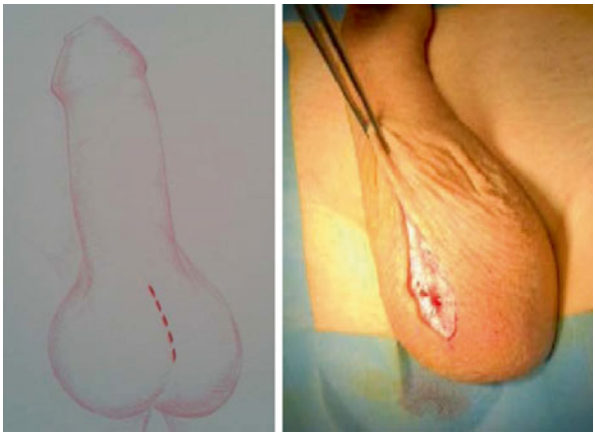

Fig. 16.16 Scrotal incision

circumcise and we cannot evaluate the point of correction intraoperatively. The procedure can be performed under either local or general epidural anaesthesia. For the penile ventral curvature repair, an infrapubic transverse dorsal incision is made (Fig. 16.16) to correct a ventral curvature or when removing or cutting the plaque in Peyronie's disease.

Colles' fascia is opened with forceps, and Colles' space is expanded to separate the tissue planes. An Allis clamp is placed, and Colles' space is entered. An assistant holds a sterile centimetre ruler against one side of the penis, and the point selected for corporoplasty is then clamped. The penis is degloved through a tiny surgical breach; the urethra is meticulously mobilised and clamped with a Babcock (Fig. 16.17).

The Babcock clamp holds the fascia at the point where we will carry out the corporoplasty. The corpora cavernosa are clamped with an Allis opposite the Babcock. The tunica albuginea is completely isolated from Buck's fascia. By levering the Babcock clamp, the spongiosus-cavernosus angle is exposed, and the corpus

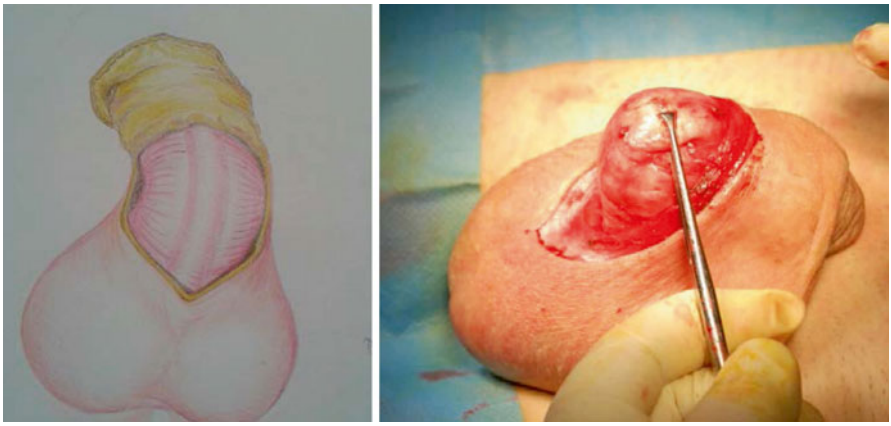

Fig. 16.17 Degloving through the scrotal access

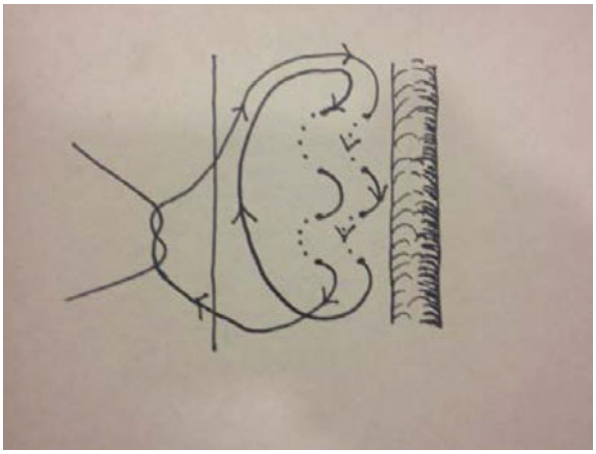

Fig. 16.18 Schematic drawing of the 'track' technique

spongiosus is separated from the corpus cavernosus for 2–3 cm. In this way the interspongiosus-cavernosus space is opened for 1 cm using forceps with the concavity downwards. This manoeuvre is performed in order to perform the corporoplasty more medially and therefore to obtain the maximum correction of the penile curvature with the minimal shortening of the penis. From the spongiosus-cavernosus angle towards the periphery, along a cleavage plane between this and Buck's fascia, a 1.5-cm undermining is performed. Then, a single 0 nonabsorbable synthetic multifilament suture is placed in order to perform a special placation on two parallel lines and therefore called 'track' (Fig. 16.18).

Along the more proximal line and parallel to the interspongiosus-cavernosus line, the suture enters the tunica albuginea and passes under it going out at a 2–3-cm

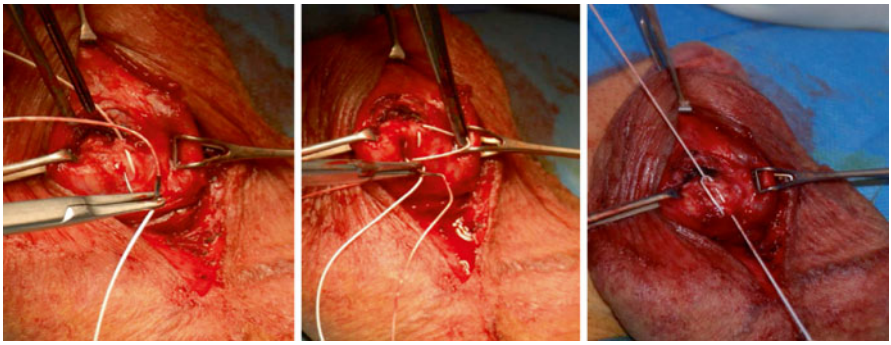

Fig. 16.19 First suture of the 'track' corporoplasty

distance to then re-enter and go out again. From the emerging point a line parallel to the passages performed is traced in the same manner entering and going out with the needle (Fig. 16.19).

Upon completion of this passage, the two ends of the suture are tied together, and the portion of tunica albuginea is doubled over the surgical knot. The distance between the entering point and the exit point of the suture minus 20 % is equal to the distance measured preoperatively in order to straighten the penis. Laterally to the corporoplasty described, two corporoplasties should be performed along the line that goes from the dorsal neurovascular bundle to the lateral end of the corpus cavernosus at 30° and 60° on the penile sagittal plane. The two corporoplasties should measure 50 % at 30° and 25 % at 60°. The suture at 30° is usually performed on a single line going in and out from the tunica albuginea and tying the knot. The corporoplasty at 60° is performed with a single suture. This asymmetry allows a uniform distribution of forces from a mechanical point of view and a better aesthetic and palpatory result. The same operative steps are performed on the contralateral corpus cavernosus. The hydraulic erection will then demonstrate the achieved correction of the curvature (Fig. 16.20).

At this point Buck's and Colles' fascia are sutured with 3-0 polyglactin suture, and the skin is sutured with 0 silk mattress sutures, which also have a haemostatic purpose (Fig. 16.21).

In cases of ventral curvature, the access is basal on the pubo-penile skin. After partially degloving the penis, a meticulous dissection of the virtual space between the dorsal neurovascular bundle and the tunica albuginea is carried out, and the first corporoplasty is performed as medially as possible [13]. In conclusion, we present our experience with an original technique for the correction of penile curvature. The basic penile access does not allow evaluation of the bending intraoperatively, as is the case with the degloving with circumcision access. Double-breasted or track corporoplasty without circumcision affords excellent correction of both congenital and acquired penile curvatures (Figs. 16.22, 16.23 and 16.24).

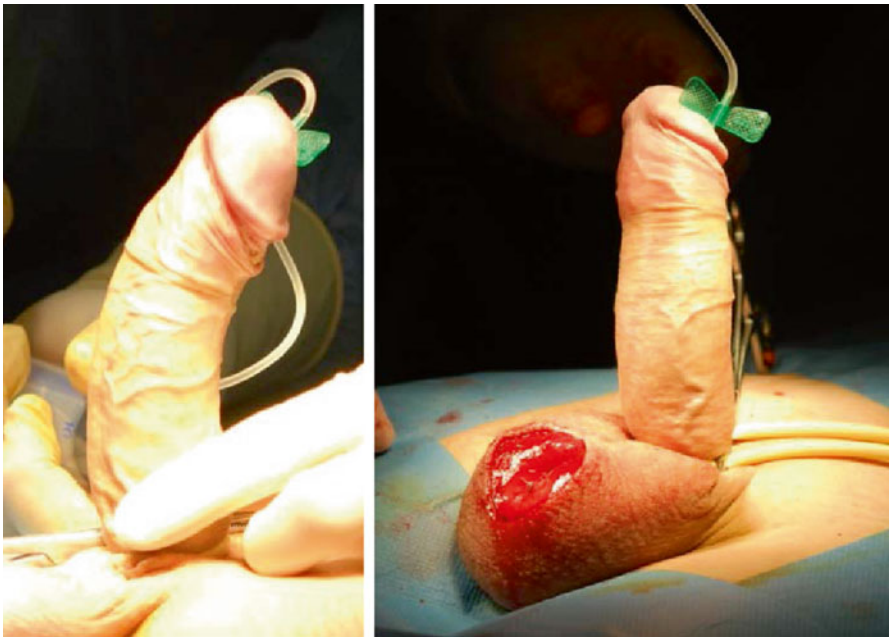

Fig. 16.20 Demonstration of the achieved correction of penile curvature

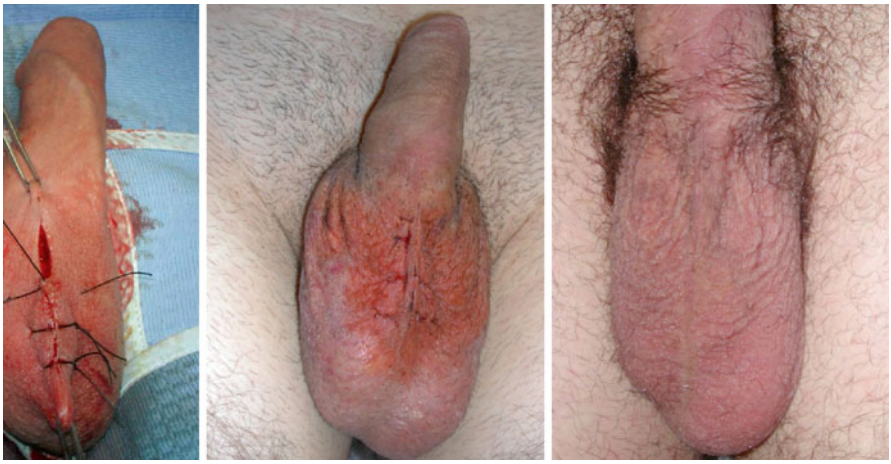

Fig. 16.21 Scrotal suture at the end of surgery, after 7 days and final result

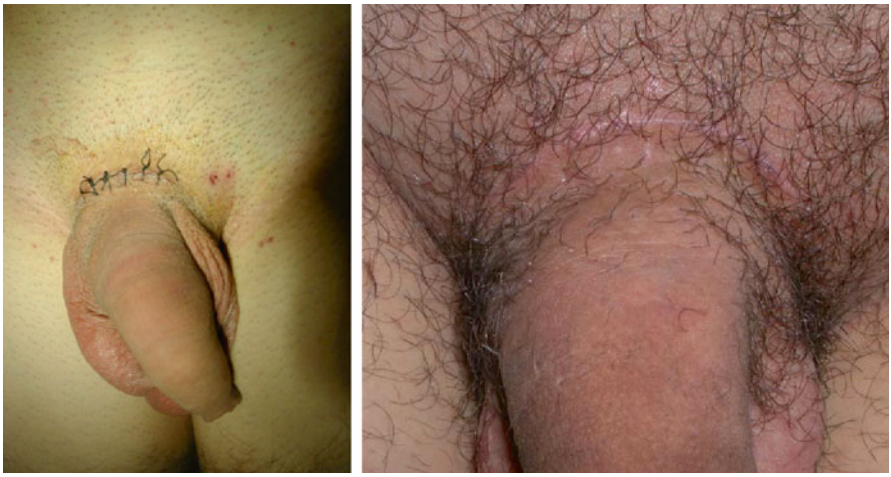

Fig. 16.22 Suture on the pubo-penile skin immediately after surgery and final result

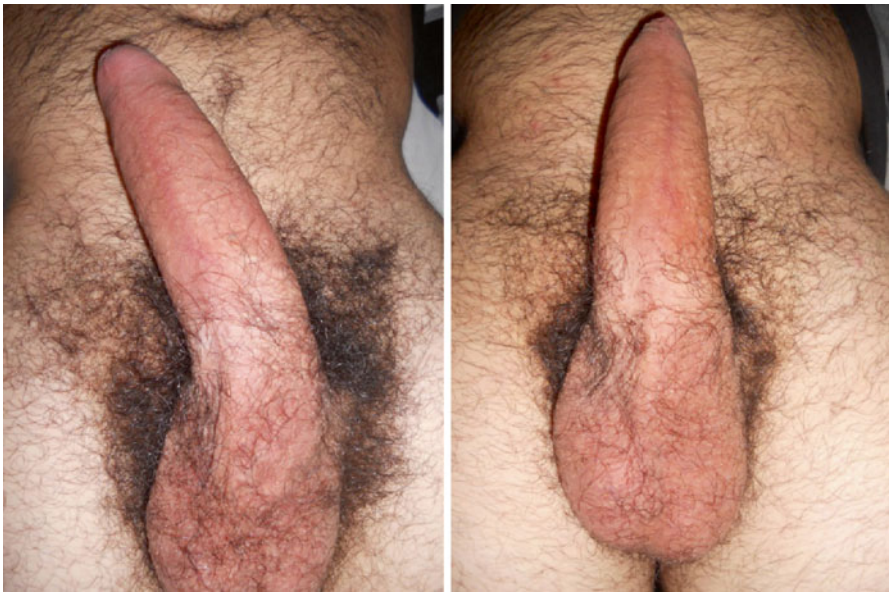

Fig. 16.23 Pre- and postoperative aspect of penile curvature corrected with a 'track' corporoplasty

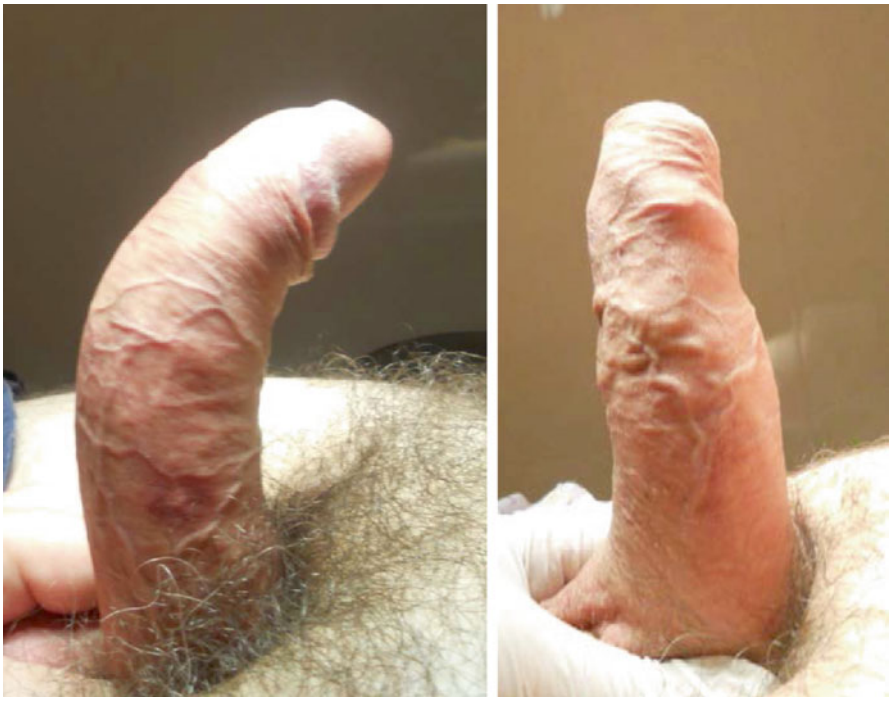

Fig. 16.24 Pre- and postoperative aspect of penile curvature corrected with a 'track' corporoplasty

Acknowledgements Special thanks to MD Nefer Fallico and MD Antonio Rossi for the collaboration in this chapter.

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Corporoplasty: Why and When

17

Alessandro Zucchi

Surgical therapy for Peyronie's disease (PD) is usually reserved for patients with stabilized chronic disease with the following objectives: to straighten and to lengthen the shaft of the penis and to restore penetrative and coital capacity. Unfortunately, the concept of "stable" disease has not yet been clarified, but it is generally accepted as there are no changes in the deformity of the shaft and no more pain during erection and/or plaque palpation from 1 year [1, 2].

Various surgical techniques exist for the treatment of PD ranging from the less invasive, which tends to correct the curvature without any direct action on the fibrous plaque, to those more complex, such as corporoplasty, which follow specific geometric criteria and use different autologous and heterologous grafts [3].

The Nesbit [4] or Yachia [5] techniques act prevalently on the convex side of the curvature, counterbalancing the lines of force caused by the plaque of the fibrosis but at the same time. The advantage of this technique, in addition to being less invasive, also reduces the volume of the corpora cavernosa, removing some forms of erectile dysfunction (ED) due to venous leakage. At the same time, the cosmetic results are not completely satisfactory because of shortening of the shaft of the penis, related to preexisting degree of curvature, which often creates notable psychological problems in these patients. Therefore, these techniques are reserved prevalently for those patients having a sufficiently long penis and having a curvature of not more than 30°/40° and for elderly patients with their associated risk factors.

On the other hand, plaque surgery calls for incision of the fibrous plaque with the aim of reducing the traction; the application of "*geometric*" *principles* represents the evolution of this procedure since the simple incision eliminates the traction but does not restore the length and girth of the penis [6–8]. In this regard, the techniques proposed by Austoni et al. [6] and Egydio et al. [7] are based on geometric

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principles with the aim of obtaining the best cosmetic and functional results. Different types of grafts (autologous and heterologous) have been proposed in these cases in order to cover the defect of the tunica albuginea, even if, currently, none of these represents the real "gold standard" [9, 10].

For example, the technique described by Egydio uses a collagenous matrix of bovine pericardium [7] and is an extremely complex procedure which requires a series of measurements with the aim of carrying out a single relaxing incision and preparing the graft in a precise manner before the implantation. This technique permits to restore the penile length and girth, even if it is extremely difficult and invasive.

On the contrary, Austoni's technique [6], which uses Virilis I®, a special silicone axial supports, is certainly simpler, and it is purposed for patients with Peyronie's disease with curvature and a slight ED or as "preventive" choice in patients over 60 years of age in whom the risk of postoperative erectile dysfunction is objectively higher (also due to the presence of comorbidities, such as diabetes, hypertension, cardiovascular pathologies, etc.). The implantation of silicone axial supports favors the extension of the shaft and permits to identify the point of the maximum curvature of the penis with extreme precision, facilitating the corporoplasty. The soft support which is implanted (Virilis I®) is not really a prosthesis in the strict sense of the word since, even after its positioning, the erection occurs spontaneously, taking advantage of the residual functionality of the cavernous tissue; therefore, it is not necessary to manipulate the prosthesis in order to obtain an erection, such as in types of semirigid or hydraulic prostheses. Furthermore, this support provides for the retraction of the graft from scarring and the formation of fibrous plaques relapse.

The original technique starts with the degloving of the penis after a subcoronal incision [6]. Two ventral corporotomies are then carried out on the proximal part of the penis. The implantation of an axial support (Virilis I® – Ø 10 Fr.) is carried out, modeling the support 2 cm longer than the length of the corpora cavernosa so as to "stretch" the penis and to easily identify the curvature (Fig. 17.1). These supports are made of silicone, are 25 cm long, and are available in three sizes (7, 10, and 12 mm Ø). Therefore, a single calibration of the corpora cavernosa is carried out using a Hegar 10 dilator to spare the erectile tissue inside the corpora cavernosa as much as possible. The insertion of the supports, in addition to identifying the curvature, also helps the surgeon to isolate the dorsal neurovascular bundles and/or the urethra according to the site of the plaque. A relaxing incision of the albuginea at the point of maximum curvature is carried out using a cold scalpel in order to remove traction, avoiding damage to the underlying cavernous tissue, which covers the silicone support inside the corpora cavernosa. The albuginea defect is covered with the saphenous vein suturing the tissue at the margins of the incision with 3/0 reabsorbable running sutures. The operation is completed with circumcision and drainage.

In a recent study of Zucchi et al. [11], the authors reported some modifications of this original technique using thinner supports (Ø 7 Fr.), modeling them just 1 cm longer than the corpora cavernosa; this technical change is useful to prevent complications, such as necrosis of the glans penis (Fig. 17.2) due to excessive traction of the neurovascular bundles. The corpora cavernosa are then dilated with Hegar 6 in order to spare as much erectile tissue as possible with the precise aim to maintain residual erection: in this way, 30–40 % of the erectile tissue is spared. The ends of the incision, carried out at the point

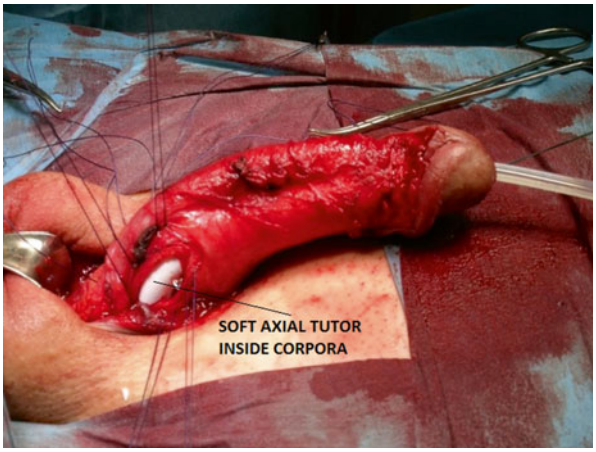

Fig. 17.1 Soft prosthesis implant showing dorsal recurvatum

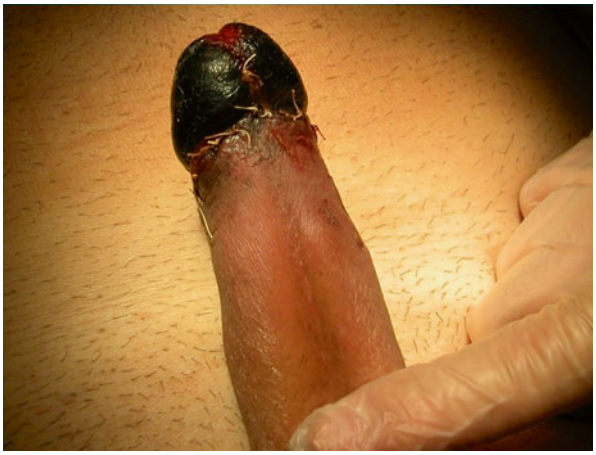

Fig. 17.2 Glans necrosis

of maximum curvature and traction of the plaque, are "dovetailed" to obtain a complete relaxation of the traction. Careful dissection of the margins of the incision is then carried out, preserving the underlying erectile tissue and as such a way as to avoid uncovering the previously positioned penile supports (Fig. 17.3). This surgical approach results in a large defect of the tunica albuginea which needs to be covered with biocompatible material (the saphenous vein proposed originally is often not sufficient); in cases of curvature greater than 50–60°, bovine pericardium or porcine dermis is therefore used since the greater the curvature, the greater the surface to be covered. One of the most currently utilized types of pericardium is Hydrix® (Assut Europe) which is particularly soft and easy to manage (Figs. 17.4 and 17.5). Regarding the results reported in this study, the average lengthening of the penis between pre- and *postoperatively* is 2 cm (range 1.2–2.3 cm) with complete correction of the curvature in all patients.

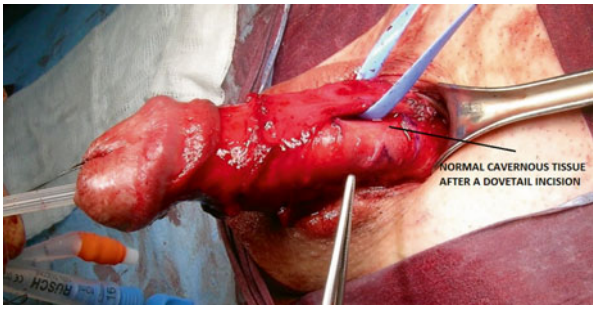

Fig. 17.3 The plaque incision is "dovetailed" and the normal cavernous tissue above completely covers the prosthesis implant

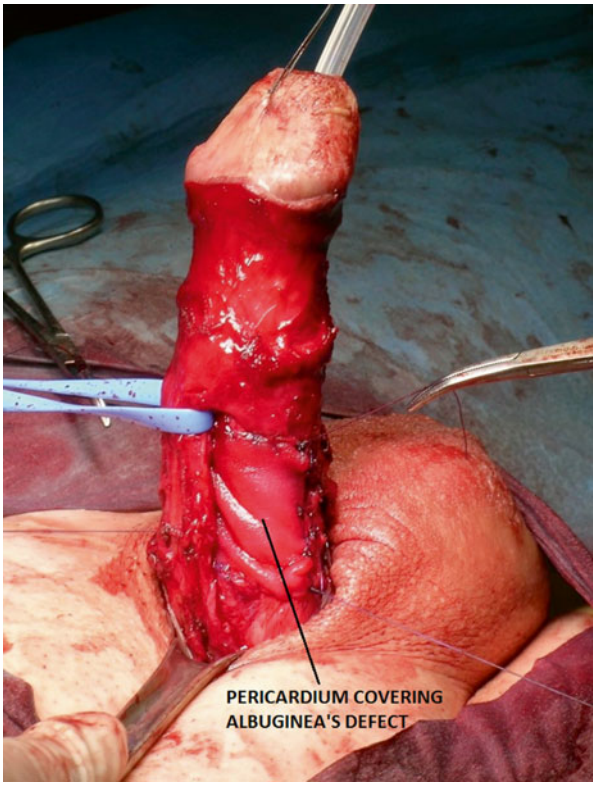

Fig. 17.4 The cavernous tissue is completely covered by a pericardial graft. The graft is sutured along the albuginea margins using running sutures

The average International Index of Erectile Function (IIEF) before surgery was 15.5, 19 after 3 months, 21 after 6 months, and 23 at 12–24 months; the evaluation of the patients and the couples using the visual analogue scale (VAS) showed good results in terms of recovery normal sexual intercourse (more than 80 % of the couples) and of the original penile length and circumference.

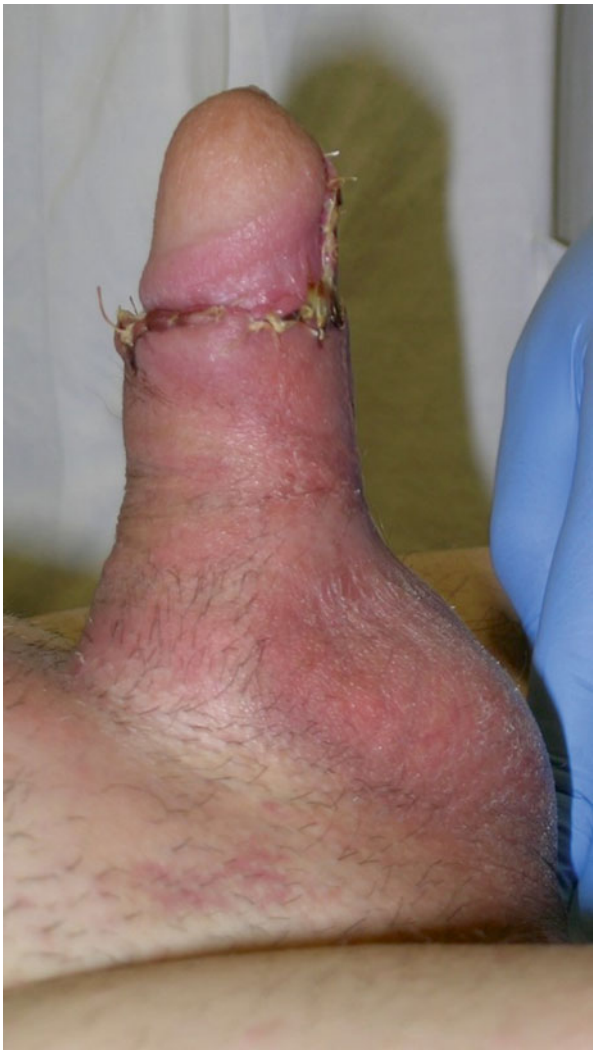

Fig. 17.5 Final result 1 week after surgery

Regardless of the type of corporoplasty used, the choice of the patch used can vary on the basis of the personal experience of the surgeon. The data in the literature regarding the patches most commonly used in plaque surgery are extremely variable and frequently not representative; for the most part, they deal with autologous (vein, dermis, buccal mucosa) or heterologous (biocompatible) materials which are extremely resistant and elastic; these materials tend to mimic the tunica albuginea avoiding scarring which could cause retraction of the graft as much as possible and, therefore, surgical failure.

In recent reviews, the use of buccal mucosa as autologous material is often cited as a second option to commercially available biocompatible tissue, and reports of clinical series using buccal mucosa are limited [12–14].

A recent review of Levine et al. [12] which includes 37 of the major case studies reported in the literature, and which includes corporoplasty with plaque incision and grafting, demonstrates how the results reported are not superior to the technique using buccal mucosa, either in terms of satisfaction or postoperative ED. In particular, in the four studies which use SIS (227 patients), three patients did not give information regarding their degree of satisfaction, while only one reported a 79 % satisfaction rate; ED ranged from 9 to 45 % [15–18]. Moreover, in the seven studies in which a pericardial graft was proposed (136 patients), the satisfaction rate was not available in four and, in the remaining three, it was reported in percentages varying from 74 to 92 % with ED varying from 0 to 30 % [19–25] as compared to 0 % ED and a 100 % satisfaction rate in the buccal mucosa graft series [14].

There are various elements in favor of the technique using a buccal mucosa graft. The inert biocompatible materials which are usually implanted (pericardium, SYS, porcine dermis, etc.) need an integration times varying from 4 to 6 weeks, the time necessary for the reconstitution of the scar tissue which is surely more "abundant" and "reactive" comparing with a living tissue, such as buccal mucosa. Buccal mucosa, thanks to its elevated binding capacity and revascularization, is immediately supplied with blood from the cavernous tissue and, therefore, being living and vital tissue, it tends to heal rapidly, immediately integrating with the surrounding albuginea tissue. Furthermore, the thickness of the buccal mucosa is nearly the same of the tunica albuginea, and this is not easy to find in the biocompatible materials currently used, which are produced in very thin sheets in order to maintain elasticity and stretching property. These intrinsic characteristics of the buccal mucosa favor easy adaptation to the margins of the graft to all sides of albuginea's incision ensuring a perfect seal. Therefore, this translates into a more rapid resumption of spontaneous erections and sexual activity of the patient and in a reduced risk of curvature relapse and ED after surgery.

Also in Egydio's procedure, where the incision could be of large dimensions, buccal mucosa can be harvested from both cheeks with two 3 × 4 cm patches.

Corporoplasty with a buccal mucosa is carried out under general anesthesia, positioning the tracheal tube, where possible, passing through the nose, in order to be able to harvest the buccal mucosa easily. After subcoronal incision and degloving, a hydraulic erection is performed positioning a 19G butterfly needle at the level of the glans of the penis and injecting saline solution inside corpora cavernosa (Fig. 17.6). The Buck's fascia is then open bilaterally, at the paraurethral level, and, in this way, the isolation of the neurovascular bundles or the urethra is carried out according to the position of the fibrous plaque to be treated. Once the site of the plaque is identified, an "I" or "H" incision is performed (dovetail incision) at the site of maximum curvature. The margins of the incision are carefully prepared on all sides, preserving the underlying erectile tissue, and the dimension of the area to be covered with the buccal mucosa is measured (Fig. 17.7). A second team harvests the buccal mucosa from the cheek and prepares the patch removing the fat (Fig. 17.8). The patch is then sutured, covering the cavernous tissue, using 3/0 reabsorbable sutures with the submucosa surface in contact with the cavernous tissue (Fig. 17.9). A hydraulic erection is then performed to control residual curvature and the straightening of the penis (Fig. 17.10). A rare complication is represented by seroma formation above the implant (Fig. 17.11).

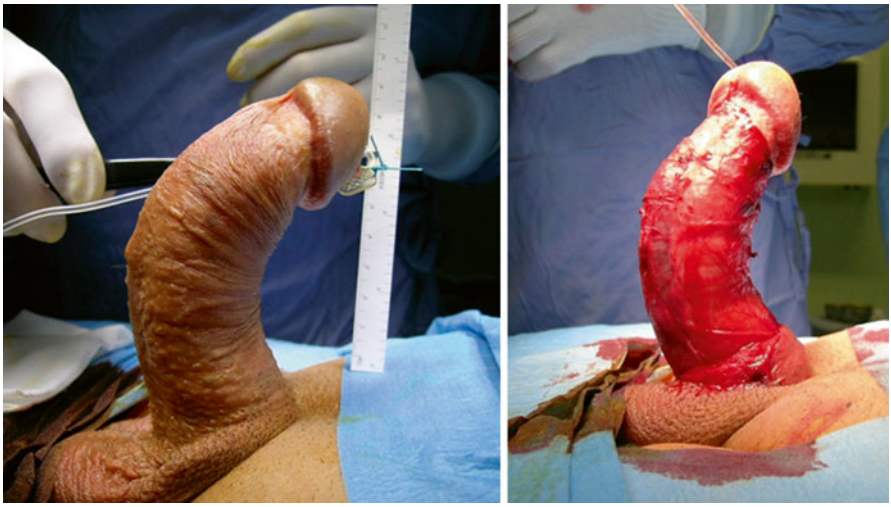

Fig. 17.6 Dorsal recurvatum after hydraulic erection (before and after degloving of the penis)

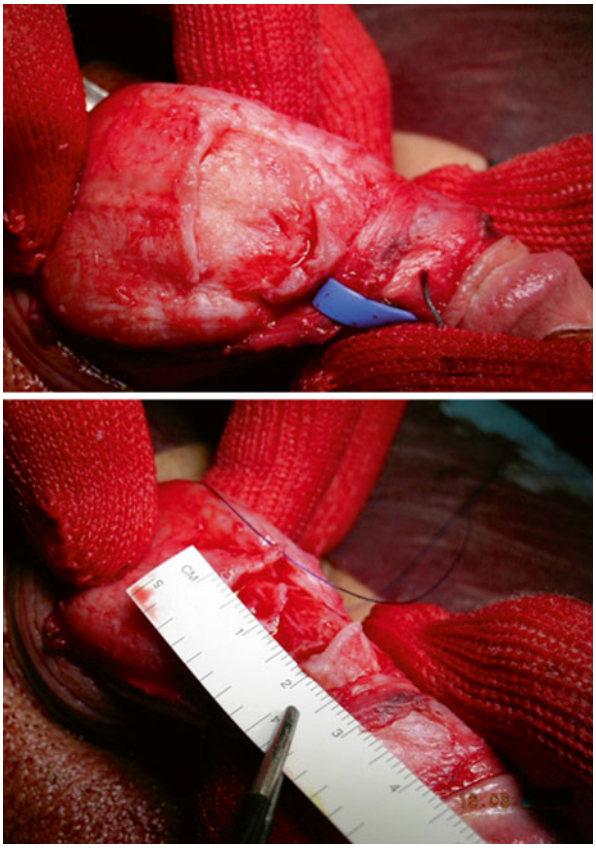

Fig. 17.7 Incision of the plaque and measurement of the size of the albuginea defect

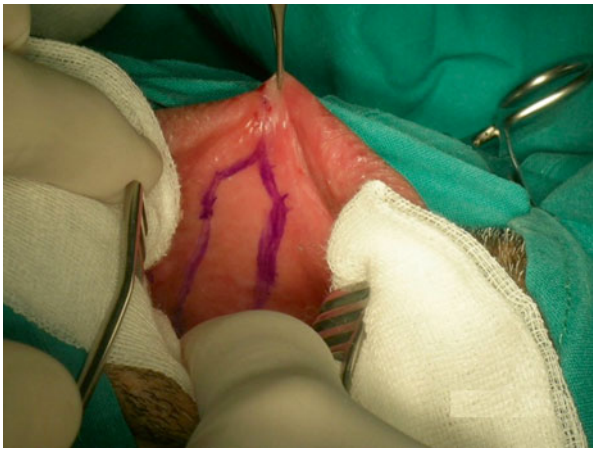

Fig. 17.8 Buccal mucosa harvest

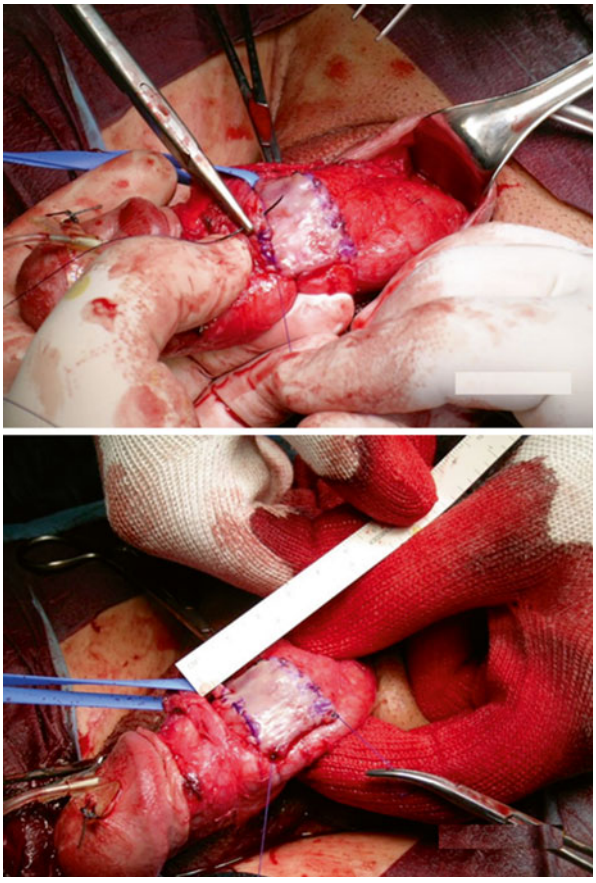

Fig. 17.9 Buccal mucosa patch is sutured along the albuginea incision margins

Fig. 17.10 Final result (the penis is completely straight)

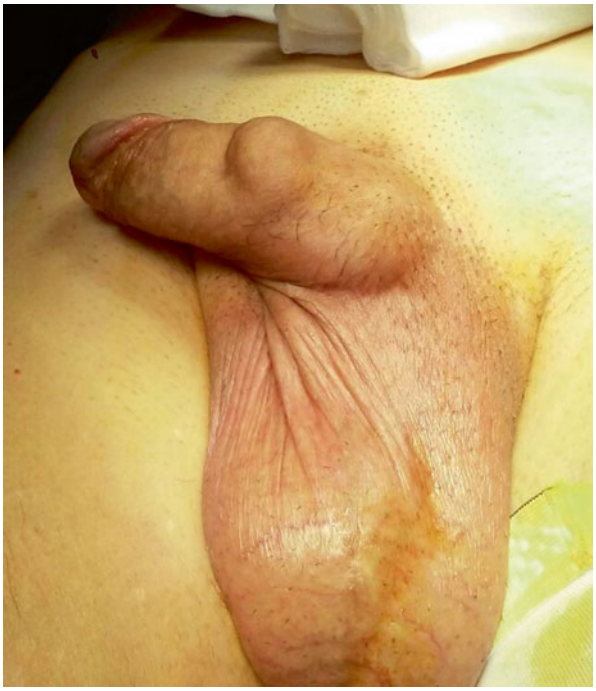

Fig. 17.11 Seroma formation 1 year after surgery

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Surgical Treatment of Peyronie's Disease by Inflatable Penile Prosthesis

18

Edoardo S. Pescatori

18.1 When IPP Is Indicated in PD

Implantation of an inflatable penile prosthesis is the treatment of choice for those men with Peyronie's disease and erectile dysfunction not responding to nonsurgical ED treatment, namely, oral medication (PDE5-Is) [12, 14–16, 19, 23, 24, 30, 33]. This allows for correcting the deformity while addressing ED as well. Although there may be some intrusion of the plaque on the corporal bodies, this does not usually cause any difficulty in the implantation [16].

It has further been proposed that, because surgical intervention without prosthesis placement can result in penile shortening and subsequent ED, the pool of candidates for prosthesis implantation should be expanded to include men with a short penis and partial erections and that all patients with PD older than 50 year, especially those with vascular comorbidities, should be counseled to consider penile prosthesis [34].

18.2 Advantages of IPP over Malleable Prostheses

Inflatable devices lead to higher functional satisfaction and lower rates of persistent penile curvature deformity compared with malleable devices [7, 8]. An inflatable penile prosthesis appears to be the preferred surgical implant, as the pressure within the cylinders allows for superior correction of curvature with manual modeling, as well as improved girth enhancement [10]. The vast majority of available literature on IPP in the treatment of PD refers to three-piece inflatable prostheses; nonetheless, there are two reports on the use of the two-piece inflatable prosthesis

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Ambicor ™ in PD [13, 14]. Both papers claimed successful straightening and no mechanical failures or infections during a mean follow-up of 39 and 43 months, respectively.

A malleable prosthesis even when it corrects the deformity gives less overall functional satisfaction [16]. Reasons for preferring inflatable devices include guaranteed girth expansion, better cosmetic appearance in erection, and normal aspect in flaccidity. One study reported a 52 % patient and 60 % partner dissatisfaction rates with malleable implants. Reasons for patient dissatisfaction included complaint that prosthesis did not mimic natural erection, persistent slight penile deformity, poor concealment of the implants, and decreased sensitivity/coldness in the glans. Reasons for partner dissatisfaction included insufficient penile girth, "coldness" of the glans, unnatural sensation attributable to the device, and dyspareunia [21]. In another study with malleable implants, one third of the partners complained of not quite natural appearance of the penis [2].

18.3 Techniques of Penile Straightening

Several are the available options to pursue penile straightening by IPP. There is a general consensus that following prosthesis insertion in the presence of a residual curvature exceeding 30°, manual modeling should be performed [36]; when the post-modeling residual curve is >30°, a plaque-releasing incision should be considered. Finally, a tunica graft is recommended to avoid implant herniation or cicatrix contracture when the defect is >2.0 cm [7, 12, 14, 30, 33]. It has been proposed that successful penile straightening be defined as end-of-operation residual curvature ≤15° [23].

The main strategies of penile straightening by IPP are summarized in Table 18.1.

18.3.1 Simple IPP Placement Without Ancillary Maneuvers/ Procedures

In most patients with mild to moderate deformity, up to 30°, insertion of a penile prosthesis tends to straighten the penis without the need of additional procedures [16, 25].

Table 18.1 Main strategies to achieve penile straightening by IPP in PD

Simple IPP placement without ancillary maneuvers/ procedures
Penile modeling over IPP
Penile modeling over hydraulic-induced erection
Tunica incision without grafting
Tunica incision with grafting

18.3.2 Penile Modeling over IPP

Manual modeling is a well-established method for correcting the majority of the persistent curvatures after implantation of the penile prosthesis. It has been proposed by Wilson in 1994 [36], and it is indicated when after IPP insertion the residual curvature exceeds 30° [12, 14, 30]. In this technique, after placement of the cylinders and closure of the corporotomies, the prosthesis is inflated to the maximum distension. Then the penis is bent forcibly in the direction opposite the curvature and the bend is held for at least 90 s. This maneuver results in splitting and rupturing of the Peyronie's plaques. Manual modeling of more than two sessions is not advised. This technique requires a high-pressure cylinder with limited girth-expanding properties [7], such as AMS 700™ CX and Coloplast™ Titan. Rubber shod hemostats should be applied to the tubing between the pump and the cylinders to protect the pump from high pressures during the maneuver. Urethral injuries while performing this technique by distal extrusion of the prosthetic cylinders at the fossa navicularis have been reported [34]. With this technique alone, Wilson achieved successful straightening in 86 % of his patients [36]. Montague reported that all his 34 patients with AMS 700™ CX and modeling had complete correction of curvature [18]. At 5-year follow-up, long-term curvature correction was present with no higher incidence of device revision in modeling compared to surgery without modeling [35].

18.3.3 Penile Modeling over Hydraulic-Induced Erection

The feasibility of intraoperative penile modeling over an artificial erection, before prosthesis placement, has been recently proposed. Following hydraulic erection, similarly to the classic Wilson' maneuver, a forceful penis bent applied in a direction opposite to the curvature and repeated two times followed by a bicomponent inflatable prosthesis (Coloplast Excel™) insertion produced a complete penile straightening [27].

18.3.4 Tunica Incision Without Grafting

When the post-modeling residual curve is >30°, a plaque-releasing incision overlying the area of maximum curvature after elevating Buck's fascia in that area should be considered [4, 14, 30]. Single or multiple small incisions can be performed [20, 22]. The transverse penoscrotal skin incision will allow access to virtually the entire shaft, except when the curvature is distal on the shaft, so degloving the penis is not always necessary [10].

Electrocautery can be used safely to incise the tunica albuginea above any underlying inflatable cylinder. To avoid electrocautery injury, the cylinder should be deflated before electrocautery, and the coagulation intensity current should set at 35 W. The electrocautery should be applied only to the outer tunical layer, not to the

whole thickness of the tunica. Afterwards, the cylinders are reinflated, the plaque is split by bending the penis, and further modeling can be performed to optimize deformity correction. Effort should be made to preserve the cavernosal tissue over the implant [8]. When Coloplast™ cylinders are used, the energy should be less than 30 W to reduce potential cylinder injury [6].

18.3.5 Tunica Incision with Grafting

Grafting over the albuginea defect is generally recommended when the defect measures greater than 2 cm in any dimension to prevent cicatrix contracture of the incision or herniation of the prosthesis [12, 14]. Puri and Hellstrom suggested incision and grafting in men with more severe penile curvatures (>60°), large dorsal plaques (>4 cm), ventral plaques, or residual curvature after manual modeling [29]. Historically, several synthetic grafts have been used; currently, biografts of autologous rectus fascia, cadaveric pericardium, and porcine jejunal submucosa are recommended [7, 10]. Use of locally harvested dermal grafts is not recommended, as there is risk of transferring bacteria to the prosthesis [30]. The selected graft is assembled to the tunica albuginea with long-term absorbable sutures.

18.4 Before Surgery 1: Addressing Penile Retraction

A recent small pilot study using traction therapy before penile prosthesis placement in men with PD and penile shortening demonstrated that, following 3–4 months of daily traction for an average of 3 h or more per day, there was no further loss of length after prosthesis placement, and the majority of patients had gained some length (0.5–2.0 cm) compared to their pre-traction stretched length [11]. Daily vacuum therapy for several months before IPP placement has been advocated: preliminary studies suggest that preoperative stretching with vacuum may allow longer cylinder placements at the time of the penile prosthetic surgery (Paradiso M, 2011, personal communication) [26].

18.5 Before Surgery 2: Surgeon-Patient Interaction

Literature data show excellent results of inflatable penile prosthesis in PD cases, provided men have realistic expectations [28]. Accordingly, preoperative counseling and setting appropriate expectations as with any prosthesis placement are critical [1], along with shared decision-making after published algorithms and guidelines and obtaining preoperative informed consent [4, 30].

The most common postoperative complaints in men who undergo penile prosthesis placement are length loss [17], incomplete penile straightening, and diminished penile sensation [9].

Wang first reported penile length decreases of 0.8, 0.75, and 0.74 cm at 6 weeks, 6 months, and 1 year, respectively, following IPP surgery [32]. Any possible postoperative length loss due to the implant may be distressing to the patient and should be addressed preoperatively.

Preoperative discussion should also be focused on the goal of obtaining "functional straightness," in which a residual curvature of 20° or less in any direction would likely not compromise sexual activity [9].

Penile hypoesthesia may occur in up to 20 % of cases, especially if the neurovascular bundle has been mobilized during surgery; diminished penile sensation is usually transient, but occasionally it may impair ejaculation and orgasm. It is accordingly appropriate to discuss this possible event with the patient, preoperatively.

18.6 After Surgery

It has been recently proposed that reduced length of the penis after IPP implantation can be caused by the pseudo-capsule that would limit the elongation of the prosthesis and of the penis; early device activation resulted effective to maintain the preimplant penile length after the prosthetic hydraulic implant versus a reduced length in the group with delayed activation [3].

18.7 Outcomes

The success rate with IPP in PD ranges from 84 to 100 % in terms of straight penis and low complications [12, 14, 31]. Satisfaction rates are similarly high: Levine reported that 91 % of patients were satisfied with concealability, 84 % were satisfied with ease of inflation, and 71 % had no difficulty with deflation. Additionally, 60 % of patients reported that their partner was either very satisfied or somewhat satisfied with their outcome [12]. A study comparing patient satisfaction after implantation with either the AMS 700™ CX or Coloplast™ Titan IPP reported that both devices provide permanent penile straightening and high patient satisfaction, without an increased risk of revision surgery [5].

Reported complications after penile prosthesis implantation for PD are prosthesis and wound infection, urethral perforation, decreased penile sensation, penile shortening, delayed ejaculation, and mechanical failure [8].

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Surgical Techniques for Difficult and Complicated Cases of Peyronie's Disease

19

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Peyronie's disease (PD) is the result of the formation of fibrous plaques in the tunica albuginea of the penis. Typical presentations of PD are represented by pain during erection, erectile dysfunction and penile deformities [1–3]; the latter manifestations are often major factors in conditioning surgical management of the disease.

PD has a severe impact on patients' relational and sexual life, and it's often associated with depression; as a matter of fact, this disease has been demonstrated to be associated with devastating emotional, sexual and relationship effects [4, 5].

Pain is an early and unsteady sign, usually regresses spontaneously and sometimes is improved by medical therapy [6]. However, in very few cases, it represents a clinical problem.

Erectile dysfunction can be treated pharmacologically (typically by phosphodiesterase-5 inhibitors, less frequently using intracavernous injection) only when axial deviation and penile deformity are mild or not so severe to impair penetration; in patient not responding to oral therapy, the placement of a penile prosthesis should be considered.

Penile deformities include curvature, narrowing and penile shortening.

When penile deformation is mild and there's a good erectile function (or even a mild ED with a good response to oral therapy), a medical approach is suggested. Among the medical treatment, intralesional injection of verapamil has been widely used [7]. Recently the collagenase clostridium histolyticum injection has been approved by the US Food and Drug Administration (US FDA), and published studies demonstrated a statistically significant improvement from baseline of penile curvature deformity (34.4 %) [8, 9]. Particularly interesting, from a surgical point of

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view, the recent report by Laurence that collagenase treatment does not jeopardize surgical treatment for PD: in a small series of patients, straightening surgery has been used to manage residual curvature after collagenase injection treatment without any anatomical difficulties or complications secondary to the effects of the medical treatment [20].

In patients not responders to medical therapy, a surgical management should be adopted. Patients with a good erectile function and moderate penile deformities can be surgically treated by Nesbit-like techniques [10–13]; patients with severe deformities need a plaque surgery, with or without placement of a penile implant [14–19].

Difficult and complicated cases in the surgical management of Peyronie's disease are mainly based on an extensive tunical fibrosis. Scarring process due to Peyronie's disease in some patients is very extensive and involves the septum and the cavernous tissue under the tunica; these cases present often hard difficulties in the dilation of corpora cavernosa that can be solved using scissors or particular dilators with edges to cut fibrotic bundles within the corpora (as Rossello or double-bladed advanced cavernotome). When the fibrotic tissue results particularly hard, the dilation can't reach an intracavernosal diameter proper to contain two standard cylinders; in these patients could be useful the implantation of prosthesis with a reduced diameter. The main brands of prosthesis have in their catalogue special models for these applications, and the surgeon should check to have in the operatory room the complete set when approaching a Peyronie's disease case.

When the extensive scarring involves the whole circumference of the penis and the septum, the main problem is a penile shortening rather than angulation. We believe that penile shortening is the real challenge in surgical procedures for IPP.

An extensive fibrotic involvement of tunica albuginea, in addition to PD, may also be the outcome of a specific scarring reaction following a number of situations, such as poor outcome of an andrological surgical procedure or a prosthetic infection or even a long-lasting stasis priapism. For example, Nesbit-like procedures are considered a safe solution to penile bending, but in some cases, their outcomes include an unacceptable penile shortening: namely, if a Nesbit-like technique is applied to cases with a penis already too short prior to surgery and/or too bent or if the disease itself has been evolved after the procedure with a new fibrotic poussee, the penis can result too short to satisfactory sexual intercourse and demands a further surgical solution.

When the lenght of the shaft results less than 6-7 cm, achieving sexual intercourses can be extremely challenging, even after penile prosthesis implantation (PPI): in this case, the penile prosthesis implantation achieving sexual intercourses can be extremely challenging; in this case, the penile prosthesis implantation as a unique procedure can't provide a penis length adequate for penetrative sexual intercourses, and a penile lengthening procedure should be applied.

The treatment of severe penile shortening associated with erectile dysfunction is still nowadays a surgical dilemma. Lengthening strategies can be divided in two groups: procedures that don't require an incision of the tunica albuginea and

techniques that require one or more incisions of the tunica and the placement of a graft.

Among penile lengthening procedures with corporoplasty, the following techniques are noteworthy (for historical reasons or for widespread application)

- Penile extender or vacuum device
- Suspensory ligament incision
- Pubic fat excision
- Apollo tissue expander
- Lengthening penile inflatable prosthesis (AMS 700 LGX)

Among penile lengthening procedures with corporoplasty are noteworthy, for historical reasons, results and widespread application:

- Rigaud procedure
- Paulo Egydio procedure
- Sliding technique

The previous techniques can be associated one to another according to the severity of the penile shortening and the physical characteristics of the patient; typically the incision of the suspensory ligament is a simple and safe manoeuvre that can be usefully associated with a number of other procedures.

19.1 Penile Lengthening Procedures Without Tunica Albuginea Incision

Recently, the use of penile extenders, employed to stretch the penis under a gentle tension, has been introduced in the clinical practice, recording in some cases an increase in penile length. The device needs to be placed from 5 to 9 h per day for 6 months; the increases in penile length are usually moderate, with an average of 1 cm (range 0.8–2 cm), so this solution can't be suitable to treat severe shortenings [21–24].

Among the surgical strategies, the division of the suspensory ligament can result in a slight lengthening of the free portion of the shaft, although it doesn't give a real lengthening of the corpora cavernosa; this technique, as previously said useful in combination with other procedures, has a low rate of satisfaction when performed as a unique procedure [25].

In selected patients with a significant suprapubic fat, a liposuction of the fat and an abdominoplasty can be considered to increase the length of the free portion of the shaft [26]. As a matter of fact, the more the suprapubic fat is represented, the more satisfying are the cosmetic results, and it has a clear indication only in patients with abdominal obesity or with genital lipodystrophy.

19.2 Penile Lengthening Procedures with Tunica Albuginea Incision

An effective solution for cases of real and moderate to severe penile shortening is the implantation of a temporary intracavernous expander ("Apollo" expander, Giant Medical Corporation, Cremona, Italy). The device is formed by two cylinders inserted in the corpora cavernosa with the same approach normally used in non-inflatable penile prosthesis; each cylinder can progressively increase its length by the percutaneous injection of saline solution in a chamber positioned on the apex. Repeated injections (some cc of saline every 2 weeks) provide a progressive increase of the length of the corpora, without any traumatic traction. Since 2008 we implanted the Apollo [27] expander in 18 patients affected by PD associated with severe erectile dysfunction. Starting from 1 month after surgery, the injection of the device was performed every 2 weeks, and the expansion was continued until the patient was satisfied of the length of his penis (the maximum lengthening provided by the device is up to 5 cm; in our series the mean gain in penile length was 3.5 cm). From 6 to 8 months after the implantation, the Apollo can be substituted by a definitive penile prosthesis, either inflatable or non-inflatable. In our series, no intraoperative nor postoperative complications were detected, and no technical difficulties in the prosthesis substitution were reported. According to our experience, the use of the Apollo tissue expander can provide a real lengthening of the shaft but on the other hand requires two surgical procedures and several inflation sessions on an outpatient basis: a considerable high compliance of the patient is thus necessary.

In patients with a mild penile shortening that require the positioning of an inflatable penile prosthesis, a new model of penile implant (AMS 700 LGX TM) recently proposed by the American Medical Systems can be used. The prosthesis provides during activation up to 20 % gain in length; we believe that this device can't solve a unique procedure cases of severe retraction, but it can be useful in mild penis shortening.

Since the first report of Rigaud and Berger in 1995, circular relaxing incisions, apposition of one or more patches of various materials and positioning of a penile implant has been widely employed and accepted for the treatment of severe shortening with erectile dysfunction [28, 29].

In 2013 a paper by the same author reported an evolution of the Paulo Egydio technique for penile straightening, designed to obtain, when possible, a further lengthening effect. The technique consists in continuing the relaxing incision, performed on the basis of geometrical principles previously described, with a semicircular incision on the opposite side of the penis, thus obtaining a complete circular interruption of the tunica albuginea [30–32].

All the procedures based on circular incision of the tunica provide a real and consistent lengthening of the penis; the width of the gap after the albugineal incision and the positioning of the prosthesis is almost equal to the real improvement in the length of the penis. The major limiting factor of the lengthening effect of the procedure is the length of dorsal neurovascular bundle (and, with a much lesser importance, the urethral complex): the bundle is quite inextensible; however, it can't be

subjected to tensile stress without serious risks of hypoesthesia/anaesthesia or even ischaemic necrosis of the glans. Moreover, in complicated PD cases, the bundle is often involved in the fibrotic process and is quite shorter than in normal conditions. So the stretching of the penis and the choice of the right length of the prosthesis to be implanted are among the most delicate key steps of these procedures. In particular, it has to be noticed that every manoeuvre on the penis after the circular incision of the tunica, in particular the dilation of corpora cavernosa, requires utmost care and delicacy because every longitudinal traction directly stresses the neurovascular bundle, since the continuity of the albugineal skeleton of the penis has been completely interrupted.

19.3 Sliding Technique

In 2012 we proposed our personal technique to manage penile shortening secondary to Peyronie's disease. The principle of this approach is an original ventro-dorsal incision of the tunica albuginea, providing a satisfactory lengthening and an early stabilization of the penis, preventing axial tension on the neurovascular bundles during the procedure [33].

The first steps of the procedure are the standard manoeuvres of degloving of the penis and isolation of the dorsal neurovascular bundle and the corpus spongiosum of the urethra: the first circumferential subcoronal incision is made, and the penis is degloved to the penile root and then is extracted from the skin through a second penoscrotal incision. The Buck's fascia is then longitudinally incised at the sides of the corpora cavernosa, and the neurovascular bundle is isolated in centripetal direction, for almost the entire length of the penis to be able to get the maximum elongation. Then the corpus spongiosum of the urethra is separated from the corpora cavernosa. Two longitudinal incisions of the tunica albuginea are then carried out on the lateral sides of the two corpora cavernosa: the first incision at 3 o'clock on the left and the second incision at 9 o'clock on the right. The length of the incision should be adapted to the possible stretching of the neurovascular bundle; usually a 4 cm lateral incision can provide the maximum lengthening allowed by the neurovascular bundle. A dorsal semicircular incision is made to connect the distal ends of the lateral incisions, and a second semicircular ventral incision is made to connect the proximal ends of the lateral incisions (Figs. 19.1a and 19.2).

After the dissection of the tunica albuginea from the cavernous tissue and from the septum, a gentle traction is exerted on the glans, thus obtaining a sliding of the ventral/distal part over the dorsal/proximal one and therefore a real lengthening of the penis. The stretching is arrested when the neurovascular bundle reaches the maximum length. At this point, two 3/0 polyglycolic sutures are applied between the two lateral portions of the albuginea still mated (Figs. 19.1b and 19.3).

Two rectangular- and bow-shaped defects of tunica albuginea remain: the first one, ventral and proximal, and, the second one, distal and dorsal. From the proximal part, dilation of both corpora cavernosa and the measurement of their length are performed with Subrini's dilators. This dilation can be easily

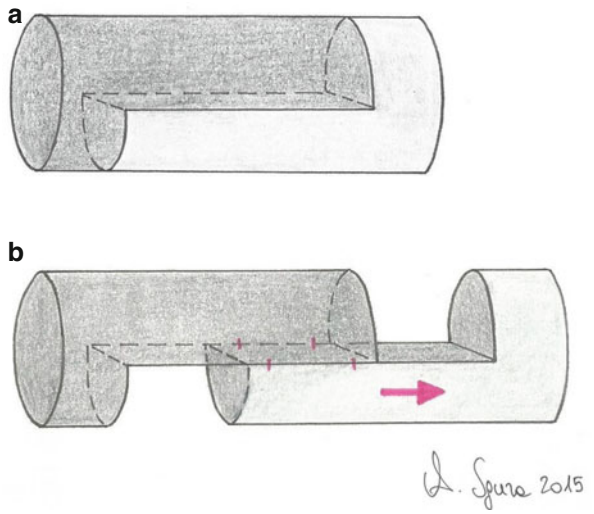

Fig. 19.1 A schematic view of the procedure. (**a**) 4 cm longitudinal incisions of the tunica albuginea are carried out on the sides of the two corpora cavernosa; then two semicircular incisions are made at the opposite ends of the longitudinal incisions. (**b**) sliding of the ventral/distal part over the dorsal/proximal one and application of sutures between the two lateral portions of the albuginea still mated

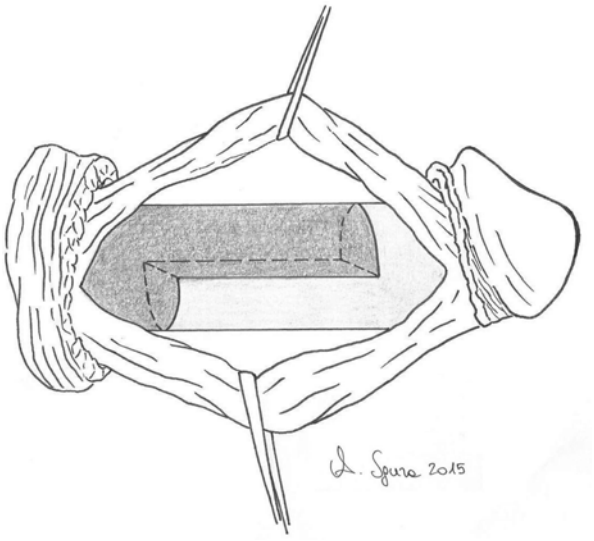

Fig. 19.2 The incisions of the albuginea from the right lateral view of the penis

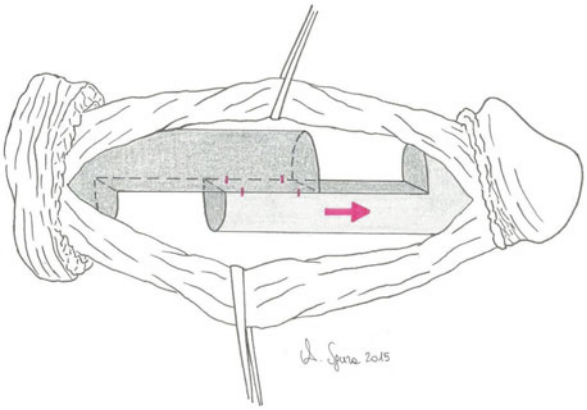

Fig. 19.3 Sliding of the ventral/distal part over the dorsal/proximal one until the dorsal neurovascular bundle reaches the maximum length; application of sutures between the two lateral portions of the albuginea still mated

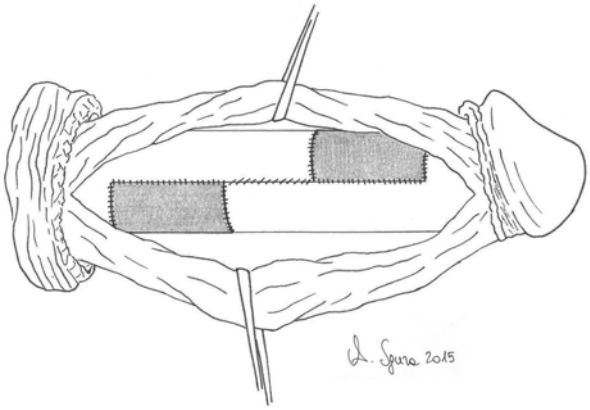

Fig. 19.4 The final result after the two losses of substance are covered with two rectangular grafts

performed without the risk of longitudinal traction on the neurovascular bundle or urethra, as the distal and proximal part of the penis are well established by the sutures on the two longitudinal incisions previously applied. The two losses of substance are then covered with two rectangular grafts (Fig. 19.4). In the case of an inflatable penile prosthesis implantation, we suggest to place the double-patch graft before inserting the two cylinders in the corpora cavernosa, in order to prevent the risk of damaging them during the suture of the patches. The two cylinders of the prosthesis are easily inserted in the two corpora cavernosa by

the same proximal defects or by additional proximal incisions if an inflatable penile implant is used, in order to provide a proper path for the tubing system. The operation ends with reconstruction of the Buck's fascia, re-gloving and circumcision.

The technique first has been tested in a pilot mono-centre study at University of Turin; then several centres in Italy and around the world adopted the technique, confirming favourable.

A retrospective, international and multi-institutional study proposed by our group evaluated surgical outcomes and satisfaction rate in patients treated in the last few years with the sliding technique for end-stage PD with severe shortening of the shaft. Twenty-one patients affected by end-stage Peyronie's disease, with severe erectile dysfunction, a significant shortening of the shaft and a curvature less than 30°, were selected in four European andrological centre. In all patients, the sliding technique as described in the original paper was performed and a penile prosthesis was implanted: in 16 cases an inflatable prosthesis (14 AMS 700 CX Inhibizone and 2 Titan Coloplast) and in 5 cases a non-inflatable prosthesis (AMS Spectra). Intraoperative and postoperative complications were recorded, and patients were asked to fill IIEF and EDITS questionnaires 1 year after the procedure (minimum follow-up 13 months).

The operative mean time was 2 h and 50 min. Nor intraoperative major complications were detected. The procedure resulted in a mean real lengthening of the shaft of 2.9 cm. Two postoperative complications were reported, a glans partial necrosis (with spontaneous restitution ad integrum) and an infection of the prosthesis that required the removal of the penile device. The mean IIEF score (all domains) at 1-year follow-up was 58.2, whereas the EDITS was 47.

These data confirms that the "sliding technique" is an effective and reliable procedure for end-stage PD associated with erectile dysfunction and severe shortening of the shaft to obtain a real lengthening of the penis.

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Future Perspectives in Peyronie's Disease

20

Gianni Paulis, Giorgio Cavallini, and Giovanni Alei

The underestimated occurrence of *induratio penis plastica* (IPP) along with its consequences on the erectile function and the complications of current treatments has led to the research of new medical and surgical therapeutic strategies.

The studies on the initial insult that leads to the formation of the plaque may identify the etiologic agent of IPP and result in the development of targeted therapies aiming to prevent or arrest the pathological process in its early phase.

The research can also be aimed toward a minimally invasive surgical approach in addition to the reduction of the penile shortening and the resolution of the associated erectile dysfunction.

20.1 Stem Cell Treatment

Stem cells have the capacity to divide and either self-renew or differentiate into phenotypically and functionally different cells. In humans, there are two main types of stem cells: embryonic stem cells, derived from the inner cell mass of blastocysts, and adult stem cells, which have been identified in many organs and tissues. Stem

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cells obtained from mature adult tissues are referred to as adult stem cells. Therefore, adult stem cells have the potential to become any type of cell.

The most common available sources of stem cells in adults are bone marrow and fat.

Stem cells are currently used only for bone marrow transplantation-related diseases like leukemia, aplastic anemia, and autoimmune diseases [1–4].

Significant therapeutic effects were obtained from bone marrow stem cells in ischemic lesions of the limbs, heart, and retina in vitro and in humans and in animal models [5–10].

Research into stem cell therapies for Peyronie's disease (PD) is still at a very early stage, and treatments using mesenchymal stem cells in humans are actually limited and reported as small series without ongoing multicentric randomized formats completed at this time.

However, several possibilities for their use in the clinic are currently being explored.

At first, bone marrow mesenchymal stem cells (BMSCs) were investigated for their potential in tissue repair and regeneration. The first studies were directed to stem cell treatment for erectile dysfunction [11–13]. Subsequently, adipose-tissue-derived stem cells (ADSCs), another type of mesenchymal stromal cells with a perivascular location in the adipose tissue, have become a most important resource in the field of stem cell therapy. Similar to BMSCs, ADSCs are multipotent, self-renewing cells with potential to differentiate into several cell types. Moreover, ADSCs are more abundant and easily accessible, and they can be obtained in large quantities at low risks [14]. In particular the adipose tissue yields far more stem cells than the bone marrow on a per gram basis (5,000 vs. 100–1,000) [15].

Albersen et al. [16] reported beneficial functional effects of ADSC therapy on erectile function in a rat model of cavernous nerve injury. The beneficial functional effects were accompanied by reduced fibrosis in the corpus cavernosum and a significant preservation of smooth muscle content [16]. Fandel et al. [17], in their experimental rat model of intracavernous injection of ADSCs, have reported an improvement of the smooth muscle-to-collagen ratio in the corpus cavernosum [17]. Also Qiu et al. [18] in their rat model study, after intracavernous injection of autologous adipose-derived stromal vascular fraction (SVF), have shown a decrease of fibrosis in the corpus cavernosum [18]. Castiglione et al. [19] were the first researchers to test stem cell therapy in a rat model of Peyronie's disease [19]. In this study, the authors showed that injection of adipose-tissue-derived stem cells (ADSCs) into the tunica albuginea (TA) during the active phase of PD prevents the formation of fibrosis and elastosis in the TA and corpus cavernosum.

The exact mechanisms of the antifibrotic effects of mesenchymal stem cells (MSCs) are still not known. A study of Chamberlain et al. [20] hints at immunomodulation, limiting host response to injury and therefore preventing the onset of fibrosis [20]. Other authors proposed the mechanism of induction of phenotypical changes in resident fibroblast by reduced collagen and increased hyaluronic acid production [21, 22].

Huang et al. [23] proposed that antifibrotic action of mesenchymal stem cells is due to the release of an antifibrotic enzyme, MMP-9, that appears to loosen the compact collagenous tissue [23].

Cerruto et al. [24] hypothesized that the therapeutic action of mesenchymal stem cells is due to their proangiogenic capacity that alters the cycle of vascular injury, ischemia, and fibrosis characteristic of the inflammatory phase of PD [24].

Gokce et al. [25] in their study on a rat model with PD [25], after intratunical injection of adipose-tissue-derived stem cells (ADSCs), showed a decrease of the expression of TIMPs and an increase in expression and activity of MMPs, resulting in preventive and therapeutic benefits of ADSC on penile fibrosis and erectile function in an animal model.

Besides Qiu et al. [18], other groups of researchers have demonstrated that mesenchymal cells within the stromal vascular fraction (SVF) of subcutaneous adipose tissue (ADSC) display an impressive developmental plasticity including the ability to undergo multilineage differentiation [26, 27]. Stromal vascular fraction (SVF) was isolated for the first time by Rodbell in 1964 using proteolytic enzymes and centrifugation [28].

The pluripotentiality of stem cells from human fat-derived SVF-like population has been described by Zuk et al. in 2001. These authors called these cells "PLA cells," because of the starting material processed lipoaspirates [29].

It must be recognized that there are problems and confusion with the nomenclature of stem cells derived from adipose tissue. Until recently, the following different terms for adipose-tissue-derived stem cells were used as synonyms in literature: adipose-derived adult stem (ADAS) cells, adipose-derived adult stromal cells, adipose-derived stromal cells (ADSCs), adipose stromal cells (ASCs), adipose mesenchymal stem cells (AdMSCs), preadipocytes, processed lipoaspirate (PLA) cells, adipose-derived stromal/stem cells (ASCs), lipoblast, and pericyte.

In order to eliminate this confusion determined by so many denominations, in 2013, the International Fat Applied Technology Society (IFATS) reached a consensus to use the term "adipose-derived stromal/stem cells" (ASCs) to name the plastic-adherent, cultured and serially passaged, and multipotent cell population from adipose tissue [30].

As adipose tissue is known to secrete several cytokines, Nakagami et al. [31] focused on the secretion of angiogenesis-related cytokines such as VEGF (vascular endothelial growth factor) from ASCs [31]. Rehman et al. [32] identified the stromal cell fraction in human subcutaneous fat as a novel source for autologous cell therapy [32].

Adipose-derived stromal cells (ASCs) represent the nonadipocyte cell fraction of adipose tissue and consist of a heterogeneous cell population that includes preadipocytes and vascular cells [32–34].

Adipose-derived stromal cells, with their capacity to modulate immunity and/or inflammation than to their differentiation potentials [35], seem to be particularly suitable for the treatment of PD.

These cells are obtained after enzymatic digestion with collagenase in order to dissociate the extracellular matrix. Subsequently, mature adipocytes are separated from the pelleted stromal vascular fraction (SVF) [35, 36].

It is worth pointing out that stromal vascular fraction (SVF) is a freshly isolated heterogeneous cell fraction, isolated from native adipose tissue or liposuction aspirates, while the adipose-derived stromal cells (ASCs) are homogeneous, plastic-adherent cell population, derived from SVF and propagated in culture (see Fig. 20.1).

Subsequent to their study in 2013, Castiglione et al. [37] were the first who tested autologous adipose-derived stromal vascular fraction (SVF) in a rat model of Peyronie's disease [37]. In this study, the authors showed that injection of SVF into the TA during the active phase of PD prevents the formation of fibrosis and elastosis in the TA and corpus cavernosum.

Lander et al. [38] are the only authors in the literature that have pioneered the use of autologous adipose-derived stromal cells (ASCs) in humans with PD [38].

They notified their experience, presenting a poster at the Conference: Western Section AUA 2013 Annual Meeting, November 03–07, 2013, Monterey, CA, USA.

Their experience is limited, but this represents the first use of ASCs in humans suffering from PD.

In their study, the authors evaluated the safety and efficacy of stromal vascular fraction combined with low-intensity extracorporeal shock wave therapy (ESWT) in five patients with documented chronic stable PD associated with erectile dysfunction. In the opinion of the authors, low-intensity shock waves create controlled microtrauma that is expected to be able to mimic these conditions and activate the stem cells through cytokine release to signal repair.

The autologous adipose tissue was obtained from mini liposuction (50 cc) in each patient. A closed system device was used for SVF procurement. SVF was deployed by intracavernosal injection into the penile plaques. Patients underwent low-intensity extracorporeal shock wave therapy (ESWT) to the penis on the day of SVF deployment, and treatments were also performed 48 h prior and after SVF injection. Patients were evaluated using Peyronie's Disease Questionnaire (PDQ) and Erectile Hardness Grading Scale (EHGS) scores at baseline and at 3 months after the treatment. Clinically significant improvement over baseline was seen in all five patients at 3 months after treatment. All patients noted subjective improvement in curvature, reduction in plaque size, and improvement in erectile function. EHGS mean scores increased from 2.0 to 3.6 at 3 months. All five patients' Peyronie's Disease Questionnaire scores decreased from mean 29.0 to 11.4 at 3 months.

As we mentioned in other chapters of this book, we believe that in the studies concerning PD treatment, subjective methods (questionnaires and palpation) should not be used only but also and mainly objective diagnostic methods such as penile ultrasound study, in order to determine precisely the status of zone of disease before and after treatment.

Although the early results using autologous adipose-derived stromal cells (ASCs)/SVF and ESWT in PD patients are very promising, insufficient numbers of patients have been treated to state that this treatment is very effective in PD.

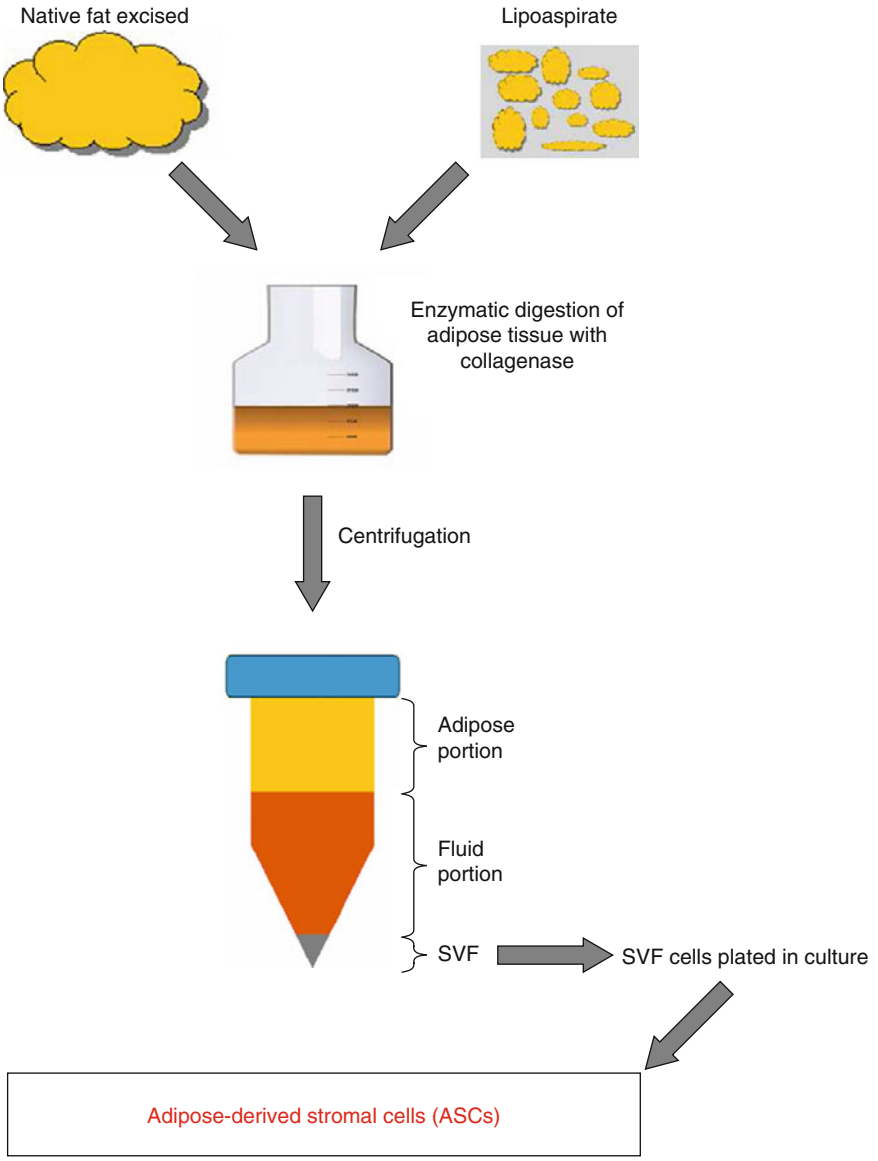

Fig. 20.1 Method of isolation of adipose-tissue-derived stromal cells (ASCs)

The only stem cell treatment explicitly approved by the FDA for use in the USA is bone marrow transplantation. The Food and Drug Administration (FDA) has not approved the use of adult stem cells/SVF for any disease including Peyronie's disease.

Despite these restrictions, in the USA the experimental studies and medical research (concerning ASCs treatment for PD) go on anyway, and they are funded

directly by patients who undergo therapy with ASCs/SVF signing and accepting an informed consent for therapy.

Although studies concerning stem cell therapy for Peyronie's disease are still in the pioneering and experimental phase, this therapeutic hypothesis seems to be the most promising for the definitive treatment of PD.

20.2 Still on the Subject of Regenerative Medicine

In view of the positive results obtained in trichology [39] and orthopedics [40], special interest is taken into the use of platelet-rich plasma (PRP) for intraplaque injections during the inflammatory stage. PRP is a blood product that has been studied for several years in many medical branches. Its rationale lies in the release of growth factors and platelet cytokines which are capable of influencing the reparative processes and regulating inflammation and neoangiogenesis. Platelets play a pivotal role in tissue repair because of the release of several different growth factors including PDGF, TGF β, VEGF, IGF-1, FGF, and EGF. The granules inside the platelets contain cytokines, chemokines, and several proteins involved in cellular regeneration, modulation of inflammation, and regulation of tissue homeostasis and regenerative processes.

During the active stage, this treatment could arrest the inflammatory process or regulate it in order to avoid fibromatosis and the associated pain.

The treatment with PRP in Peyronie's disease is not reported in the literature; therefore, we propose this approach, provided that the methodology and the effects of this treatment are carefully investigated.

As we have already been written, new treatment options could arise from the use of adipose-derived stem cells (ADSCs); however, the use of muscle-derived stem cells (MDSCs) was also proposed [41]. The MDSCs have been injected in the corpora cavernosa after an experimentally induced traumatic lesion. An et al. developed a model of penile lesion by sectioning a portion of the corpus cavernosum in the rabbit and injected the injury with MDSCs transfected with VEGF [41]. Results were evaluated with magnetic resonance imaging. The treatment determined a better cicatricial outcome and an improvement in erectile function. Although a traumatic injury of corpora cavernosa is infrequent, the possibility of using this type of cells widens the therapeutic options in reconstructive surgery, especially in cases of severe IPP.

20.3 Infiltrative Approach

In the medical approach to Peyronie's disease, several drugs have been used to arrest the inflammatory fibromatous process and the associated pain during the early stage of the pathology.

The intraplaque injection of drugs is an option that should be considered carefully, as it can contribute to the onset of the same mechanisms that lead to the

formation of the fibrosis of the tunica albuginea. Although this treatment has been banned from the guidelines by several scientific societies, currently the intraplaque injections may gain new credibility.

There are several studies proving the scientific evidence of the use of the collagenase, an enzyme produced by the bacterium *Clostridium histolyticum*, in order to break down the plaque [42–44]. Levine et al. described the intraplaque injection of collagenase *Clostridium histolyticum* (CCH) (*Xiaflex*, *Auxilium Pharmaceuticals*, *Inc*., *Chesterbrook*, *PA*, *USA*), a Food and Drug Administration-approved drug for the treatment of Peyronie's disease and Dupuytren's contracture. The authors performed up to 4 cycles of treatment every 6 weeks. The treatment consisted of two intralesional injections of 0.58 mg of CCH with a 24- to 72-h interval. Results are encouraging and complications are mainly local, which leads to think that the improvement of this technique can broaden its application. Unlike other approaches, this treatment attempts to reduce the penile shortening, which is especially important in short-size penises.

20.4 Tissue Engineering

To date, plaque surgery is complicated by a high rate of erectile dysfunction. The substitution of the portion of pathologic tunica albuginea with a patch presents several complications. Various materials, both synthetic and autologous, have been used as a patch [45]. Although autologous materials, such as small intestinal submucosa, temporalis fascia, and pericardium, do not have the problem of tolerance, they have several drawbacks such as the scarce availability, the donor site morbidity, and the limited efficacy. On the contrary, synthetic patches are easily available and moldable; however, they can generate a foreign body reaction. This can create an unpredictable retraction; that is what we wanted to avoid by placing a patch. The current aim is to create a tissue with features comparable to the tunica albuginea from a morphological and functional point of view with tissue engineering techniques.

Regenerative medicine brought very important changes in several medical fields, and it currently is the most interesting research pathway.

In this field, principles of cell transplant merge with the use of biomaterials and bioengineering, making it possible to create biological substitutes that can replace the injured tissues.

Several years ago, Schultheiss et al. [46] described the possibility of obtaining a tissue similar to the tunica albuginea that could be used as a graft. The authors isolated porcine fibroblasts from fascial biopsies and seeded them on a decellularized collagen matrix. The preparation was cultivated in a bioreactor under continuous multiaxial stress for 21 days and compared with the same cells in static cultures. Continuous multiaxial stimuli improved proliferation of fibroblasts and extracellular matrix synthesis, making this tissue suitable as a graft for penile surgery.

The expansion of the oral mucosa and its use to cover a surgically created neocavity is a method that is routinely used in male-to-female surgery with good results [47].

In the coming years, this method could become a routine operation in penile surgery avoiding the complications related to plaque surgery.

20.5 Surgical Approach

Important innovations have been described also in the surgical approach to IPP. The drive for less invasive surgical procedures has determined the evolution of penile straightening techniques, reducing the hospital stay and the complication rate as well as the costs. A further advance could result from an endoscopic surgical approach just like in other surgical branches (orthopedics, gynecology, abdominal surgery, etc.) in which such procedure has become the gold standard for the treatment of some pathologies. The localization of bending, i.e., the site for tunica albuginea plication, is evaluated by performing preoperative measurements during a drug-induced erection, as described in the two variants of Alei corporoplasty.

Two accesses of few-millimeters length allow the positioning of the optical fiber with a light source and a microcamera transmitting the image to the viewer and the instrument that permits to suture in order to obtain the plication (see Fig. 20.2). Taking advantage of the skin elasticity, the portion of penis that is operated on is lifted by a dedicated instrument, and double-breasted corporoplasty is performed.

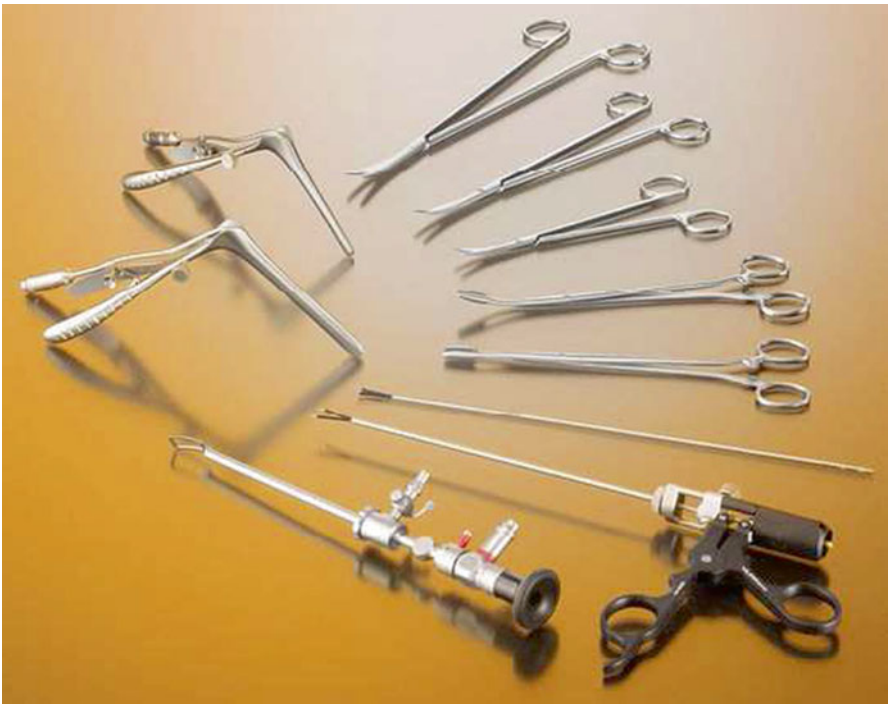

Fig. 20.2 Instruments for the endoscopic surcal approach to IPP

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